For debate

Cardiovascular effects of sulphonylurea derivatives

Implications for the treatment of NIDDM?

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Summary Sulphonylurea derivatives are widely used in the treatment of non-insulin-dependent diabetes mellitus. The mechanism of action of the insulinotropic effect of these agents is based on the closure of adenosine-5'-triphosphate (ATP)-sensitive potassium channels (K\textsubscript{ATP}-channels) in the beta cells of the pancreas. In the last decade, these K\textsubscript{ATP}-channels have been demonstrated in myocardial cells as well as in vascular smooth muscle cells. During myocardial ischaemia, the K\textsubscript{ATP}-channels are thought to open by a fall in the cytosolic ATP concentration. The increase in the extracellular adenosine concentration, and the release of endothelium-derived hyperpolarizing factor (EDHF) during ischaemia may further contribute to the opening of cardiovascular K\textsubscript{ATP}-channels. Independently from the mechanism of opening, sulphonylurea derivatives have been reported to block the opening of cardiovascular K\textsubscript{ATP}-channels. Related to the role of K\textsubscript{ATP}-channel-opening in the (patho)physiology of ischaemia, the use of sulphonylurea derivatives significantly modifies the outcome of experimental myocardial infarction. Sulphonylurea derivatives impair the recovery of the contractile function and increase the ultimate infarct size in animal models. In contrast, sulphonylurea derivatives have a beneficial effect on the incidence of ventricular fibrillation as occurs after ischaemic incidents of the myocardium. Based on these experimental observations, human studies are indicated to investigate whether the use of these drugs modifies the clinical outcome of cardiovascular events in patients with non-insulin dependent diabetes mellitus. [Diabetologia (1995) 38: 116–121]

Key words Sulphonylurea derivatives, potassium channels, cardiovascular system, adverse effects, ischaemia.

Non-insulin-dependent diabetes mellitus (NIDDM) accounts for about 85% of all cases of diabetes mellitus, and has been reported to be an important risk factor for cardiovascular morbidity and mortality [1–3]. Up to now, oral hypoglycaemic drugs, in particular sulphonylurea derivatives, have represented the backbone of NIDDM therapy for the last decades [4, 5]. The beneficial metabolic effects of sulphonylurea derivatives in NIDDM are thought to be based on an augmented release of insulin from the beta cells of the pancreas. At the cellular level, sulphonylurea derivatives exert their insulinotropic effect by closing the so-called ATP-dependent potassium channels. This in turn results in depolarization of the beta cell, which promotes an influx of calcium via the opening of voltage-dependent calcium-ion channels on the beta-cell membrane. The resultant increased binding of calcium ions to calmodulin will ultimately result in the exocytosis of insulin-containing secretory granules [4, 5].

Interestingly, several studies have shown that the cardiovascular system also shares functional ATP-dependent potassium channels (K\textsubscript{ATP}-channels) [6, 7]. Related to the important role of these channels in
the (patho-)physiological response to myocardial ischaemia, sulphonylurea derivatives have been reported to modulate the outcome of ischaemic incidents in several animal models.

\textbf{ATP-dependent potassium channels in the cardiovascular system:} Based on the results of patch-clamp techniques, and on pharmacological characteristics, the family of potassium channels can be divided into four basic groups: the voltage-gated, the ion-gated, the ligand-gated and the "second messenger/metabolite"-gated channels [8]. The K\textsubscript{ATP}-channels belong to the latter category. Several investigators have illustrated the existence of cardiovascular K\textsubscript{ATP}-channels, both in the myocardium as well as in vascular smooth muscle cells [6, 7]. Opening and closure of these K\textsubscript{ATP}-channels is dependent on the cytosolic concentration of ATP. Under physiological conditions these potassium channels are generally in a closed dormant state [8, 9]. During hypoxia and/or ischaemia, the cytosolic concentration of ATP falls which directly results in opening of K\textsubscript{ATP}-channels. Voltage-clamp studies have shown that the subsequent efflux of potassium induces hyperpolarization of the cell membrane with shortening of the action potential and with a decline in the contractile amplitude of myocardial cells [10]. In vascular smooth muscle cells, opening of K\textsubscript{ATP}-channels and subsequent hyperpolarization exerts relaxation of these cells, resulting in an obvious vasodilator response [11].

Apart from a lowering effect on the intracellular ATP-concentration, ischaemia also results in an increase of the intracellular adenosine concentration by the breakdown of ATP. During ischaemia, adenosine leaks out of the cell and stimulates specific membrane receptors of the P\textsubscript{1}-purinergic type, the so-called adenosine receptors [12]. Interestingly, a specific subtype of these adenosine receptors, the A\textsubscript{1}-receptors, have been reported to be coupled to K\textsubscript{ATP}-channels [13]. Consequently, during ischaemia K\textsubscript{ATP}-channels are not only opened directly by lowering the cytosolic ATP concentration, but also indirectly via adenosine receptor stimulation.

A third way to open K\textsubscript{ATP}-channels during ischaemia, may be the production of endothelium-derived hyperpolarizing factor (EDHF). Several studies have shown the role of the endothelium in the vasodilator response to ischaemia. It has been demonstrated that under ischaemic conditions the endothelium secretes several mediators including acetylcholine and ATP [14-16], which are both able to stimulate the production of endothelium-derived relaxing factors via, respectively, muscarinic and purinergic receptors at the luminal side of the endothelium. Apart from nitric oxide, this receptor stimulation induces the production of endothelium-derived hyperpolarizing factor (EDHF) [17]. Up to now, the structure of EDHF has been unknown, but the vasodilator properties are based on hyperpolarization, and it has been suggested that this hyperpolarization is brought about by stimulation of K\textsubscript{ATP}-channels [18].

During myocardial ischaemia three different mechanisms can contribute to the opening of K\textsubscript{ATP}-channels. First, a decrease in intracellular ATP-concentration directly opens K\textsubscript{ATP}-channels. Second, increments in extracellular adenosine concentrations as a result of ATP-breakdown may open K\textsubscript{ATP}-channels by stimulation of A\textsubscript{1}-adenosine receptors. Third, the endothelial release of EDHF during ischaemia may also open K\textsubscript{ATP}-channels. Figure 1 summarizes these three mechanisms of K\textsubscript{ATP}-channel-opening during ischaemia.

\textbf{Sulphonylurea derivatives and cardiovascular K\textsubscript{ATP}-channels:} Animal experiments have convincingly shown that sulphonylurea derivatives are able to interact with cardiovascular K\textsubscript{ATP}-channels. In vascular smooth muscle cells, this has been extensively stud-
ied by investigating the interaction between sulphonylurea derivatives and $K_{\text{ATP}}$-channel-opening drugs [19]. Potassium-channel-opening drugs comprise a group of vasodilator substances, including experimental therapeutics such as cromakalim, bimakalim and lemakalim, but also classic antihypertensive vasodilator drugs such as diazoxide and minoxidil [8]. In several animal models, sulphonylurea derivatives were able to attenuate the vasodilator response to $K_{\text{ATP}}$-channel-opening drugs [8, 20]. In the majority of these studies glibenclamide was used, but in fact other investigated sulphonylurea derivatives, such as tolbutamide and glipizide also showed this specific interaction, confirming the potency of these hypoglycaemic drugs in closing vascular $K_{\text{ATP}}$-channels. Apart from the interaction of sulphonylurea derivatives with potassium channel-opening drugs, glibenclamide has been reported to reduce resting myocardial blood flow [21].

Interestingly, in the dog, glibenclamide was also able to reduce the coronary vasodilator response to adenosine [22, 23], although the maximal response to adenosine was not affected by glibenclamide [23]. Since the vasodilator response to adenosine is thought to be mediated by the $A_2$-subtype of adenosine receptors, these data suggest that not only the myocardial $A_2$-adenosine receptors [13], but also the vascular $A_2$-adenosine receptors are at least partly coupled to $K_{\text{ATP}}$-channels. This suggestion is supported by the observation that glibenclamide inhibits the vasodepressor response to a selective $A_2$-receptor agonist in the anaesthetized dog [24]. Apart from the interaction with $K_{\text{ATP}}$-channel-opening drugs and with adenosine, glibenclamide has also been reported to inhibit the vasodilator response to endothium-dependent vasodilators such as acetylcholine and vasoactive intestinal peptide [7]. Consequently, in the vascular smooth muscle cell, all three putative mechanisms involved in the opening of $K_{\text{ATP}}$-channels during ischaemia as illustrated in Figure 1, can be inhibited by sulphonylurea derivatives.

Also in the myocardial cell, sulphonylurea derivatives are able to reduce the response to $K_{\text{ATP}}$-channel-opening. In single canine ventricular myocytes, glibenclamide attenuated the prolonging effects of the $K_{\text{ATP}}$-channel opener pinacidil on the duration of the action potential [25]. Moreover, in the isolated canine ventricle, the negative inotropic effects of pinacidil were inhibited by glibenclamide in a dose-related manner [26]. Glibenclamide was also shown to reduce the negative inotropic effects of both adenosine and acetylcholine [26], as well as the negative chronotropic effects of adenosine [23].

Myocardial ischaemia and sulphonylurea derivatives: During myocardial ischaemia, $K_{\text{ATP}}$-channel-opening may occur as a result of the aforementioned three mechanisms (Fig. 1). Animal experiments have shown that the ischaemia-induced opening of $K_{\text{ATP}}$-channels plays a role in the protection of the myocardium against ischaemia and reperfusion damage [27]. In the guinea pig right ventricular wall, pretreatment with the $K_{\text{ATP}}$-channel-opening drug pinacidil augmented the shortening of the action potential induced by no-flow ischaemia, and improved the recovery of mechanical function during reperfusion [27]. In contrast, pretreatment with glibenclamide significantly prolonged the ischaemia-induced shortening of the action potential, and after this pretreatment the myocardial preparations failed to recover mechanical function [27]. Observations in several other animal models have confirmed these results [28–30]. Apparently, opening of $K_{\text{ATP}}$-channels during ischaemia is a physiological and important adaptive mechanism for protecting the myocardium when blood flow to the tissue is compromised.

Other investigators have demonstrated that the vascular smooth muscle cell response to ischaemia is also inhibited by glibenclamide [21, 22, 31]. The post-occlusive hyperaemic response is reduced after pretreatment with sulphonylurea derivatives, and this impaired postischaemic hyperaemia may contribute to the aforementioned detrimental effects of glibenclamide during ischaemia/reperfusion injury. Within this context, the phenomenon of "ischaemic preconditioning of the myocardium" seems important. Ischaemic preconditioning was firstly described by Murray et al. [32], and concerns the fact that brief periods of ischaemia and reperfusion render the myocardium resistant to infarction from a subsequent more prolonged coronary occlusion [32]. According to the literature, adenosine receptors have an important role in this phenomenon. Animal experiments have convincingly shown that the specific stimulation of these receptors by selective adenosine analogues protects the heart against infarction [33, 34]. Moreover, prolonging the half-life of endogenously released adenosine by specific adenosine uptake inhibitors tremendously improved the mortality rate after experimentally-induced myocardial infarction [35]. The mechanism responsible for the protective effect of adenosine on the heart is not precisely known, but several potential mechanisms of action of adenosine have already been shown in man, including its direct vasodilator effect [36], its inhibitory effect on platelet aggregation [37] and on sympathetic nervous system mediated effects [38, 39], and its antiarrhythmic properties [40]. The putative coupling of $A_2$-adenosine receptors to $K_{\text{ATP}}$-channels further emphasizes the role of these channels in the pathophysiology of myocardial ischaemia, as well as the hypothetical effects of sulphonylurea derivatives during myocardial ischaemia. Indeed, a recent report has suggested that activation of $K_{\text{ATP}}$-channels is an important mechanism behind the protective effect of ischaemic preconditioning [29]. The observation that glibenc-
mide abolished the preconditioning effect of the adenosine-receptor agonist R-phenyl-isopropyl-adenosine (R-PIA) further supports the link between myocardial $K_{\text{ATP}}$-channels and adenosine-$A_1$-receptors with respect to the preconditioning phenomenon.

In contrast to the aforementioned observations, several investigators have shown beneficial effects of glibenclamide during myocardial ischaemia as far as the occurrence of ventricular fibrillation is concerned. Shortly following a myocardial infarction there is a loss of K+ from the heart, considerably increasing the extracellular K+ concentration. The conduction inhomogeneities which result from this K+ loss, and the increased likelihood of re-entry as a result of the shortening of the action potential duration probably underlie the occurrence of ventricular fibrillation and subsequent mortality within the first hours after infarction [42, 43]. Since the ischaemia-related K+ efflux is mediated by the opening of $K_{\text{ATP}}$-channels, the closure of these channels by sulphonylurea derivatives may decrease the occurrence of ventricular fibrillation during or after ischaemia [42-44].

**Hypothetical clinical implications:** Since diabetes is an important independent risk factor for the development of atherosclerotic disease, one may assume that patients with NIDDM are relatively often exposed to myocardial ischaemia. An important fraction of these patients is treated with oral sulphonylurea derivatives, and so in these particular subjects the periods of myocardial ischaemia or infarction occur in the presence of potent $K_{\text{ATP}}$-channel-blocking agents such as tolbutamide, glibenclamide or glipizide. Because of the beneficial metabolic effects of sulphonylurea derivatives, the plasma concentrations of these drugs are apparently sufficiently high to close $K_{\text{ATP}}$-channels in the pancreas. Up to now, there have been no arguments to consider these plasma concentrations too low to interact with cardiovascular $K_{\text{ATP}}$-channels. In vitro, glibenclamide concentrations as low as 0.01 μmol/l (= 5 ng/ml) were able to reduce the vascular relaxation induced by the $K_{\text{ATP}}$-channel-opening drug pinacidil [19]. In patients with NIDDM, treated by glibenclamide, plasma concentrations may reach levels above 300 ng/ml [4]. Although the free drug concentrations are probably much lower because sulphonylurea derivatives are extensively protein-bound [4], the free plasma concentrations may still be sufficient to interact with cardiovascular $K_{\text{ATP}}$-channels. Further, under ischaemic conditions, the production of lactate may lower the regional pH in the interstitium, and interestingly such an acidic condition further augments the inhibiting effects of glibenclamide on vascular $K_{\text{ATP}}$-channels [17], making low drug concentrations more effective. Despite the aforementioned considerations, it remains a critical issue whether or not the free plasma concentrations of sulphonylurea derivatives are high enough to interact with cardiovascular $K_{\text{ATP}}$-channels during conventional therapy. First, the glibenclamide concentrations as mentioned above concern peak levels, which of course will persist only for short periods after drug administration. Moreover, the concentrations which were shown to be effective in blocking vascular $K_{\text{ATP}}$-channels [19] are not necessarily high enough to interact with the more important myocardial $K_{\text{ATP}}$-channels. In this respect it has to be emphasized that differences in the pharmacokinetics between the several sulphonylurea derivatives have to be taken into account since agents with a relatively short half-life are expected to show shorter periods of high plasma levels as compared with agents which have much longer half-lives, as for example glibenclamide or chlorpropamide [45, 46]. Further, pharmacodynamic studies have shown that high dosages may counteract their purpose by reducing beta-cell sensitivity to sulphonylurea derivatives [47], suggesting that recommendations for therapeutic dosages of sulphonylurea derivatives must be lower than currently assumed, which again will reduce the chance that chronic therapy with these drugs may reveal interactions with cardiovascular $K_{\text{ATP}}$-channels. Within this context of clinical implications, it is interesting that a recently developed new sulphonylurea derivative, glimepiride, does not show an interaction with cardiovascular $K_{\text{ATP}}$-channels, this in contrast to similar studies with glibenclamide or glipizide [48]. In theory, this may lead to a generation of pancreas-specific sulphonylurea derivatives.

According to our reasoning, the treatment of NIDDM with glibenclamide or related sulphonylurea derivatives may significantly alter the response of the myocardium to ischaemic insults, and as such may influence the clinical outcome of myocardial ischaemia or infarction. The clinical implications may be two-jointed: first, sulphonylurea derivatives are thought to worsen the clinical outcome concerning the recovery of the contractile function and concerning the ultimate infarct size in patients with NIDDM suffering from a myocardial infarction. Second, sulphonylurea derivatives may have a beneficial effect on the incidence of ventricular fibrillation complicating such an acute myocardial infarction. Apart from affecting the outcome of myocardial infarction, sulphonylurea derivatives may theoretically also impair endothelium-dependent vasodilation. Since endothelial dysfunction is a remarkable feature of coronary artery disease [49], and has even been suggested to play a causal role in atherosclerosis, sulphonylurea derivatives may have a clinical impact on this level too.

It is important to question whether the currently available clinical and epidemiological knowledge on the treatment of NIDDM with sulphonylurea derivatives argues against our reasoning. Interestingly, the
UDP-G-study observed an increased cardiovascular mortality among patients with NIDDM treated by tolbutamide versus those treated by diet alone [50]. Moreover, smaller studies have also suggested a harmful effect of sulphonylurea derivatives on the outcome of myocardial infarction [51, 52]. In contrast, some investigators were not able to confirm these observations [53–55], whereas others even suggest reduced cardiovascular complications and an increased survival rate in the tolbutamide-treated group as compared with untreated or diet-treated groups [56, 57]. An extensive review report on this subject suggests that the conclusions of the majority of these clinical and epidemiological studies are not valid because of important methodological shortcomings or because of a limited statistical power [58]. Therefore, the currently available data on this item do not allow definite conclusions with respect to possible cardiovascular effects of sulphonylurea derivatives in patients with NIDDM. Especially because of the two-jointed character of the aforementioned clinical implications, with detrimental as well as beneficial aspects on the ultimate outcome of myocardial infarction, large-scale epidemiological studies will not detect such divergent effects as long as the relevant end points like ventricular fibrillation and ejection fraction are not specifically included. Current knowledge on the role of $K_{\text{ATP}}$-channels in the pathophysiology of (myocardial) ischaemia emphasizes the need for well-controlled epidemiological studies on this subject as well as for clinical pharmacological studies on the effects of sulphonylurea derivatives on $K_{\text{ATP}}$-channels in the human cardiovascular system.

Reviews on the use of sulphonylurea derivatives in NIDDM report several arguments to recommend the use of short-acting agents, at the lowest possible dose [46]. Future evaluation of cardiovascular endpoints in large-scale clinical trials may uncover whether the interaction with cardiovascular $K_{\text{ATP}}$-channels is another reason for this recommendation.

References

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