Diabetologia (1997) 40: S160–S161

Diabetologia

Cardiovascular effects of sulphonylurea derivatives

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The classical sulphonylurea derivative glibenclamide is widely prescribed for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). The mechanism of action of this drug is based on an augmented release of insulin from the beta cells of the pancreas, triggered by the closing of so-called ATP-dependent potassium channels (ATP: adenosine'5-triphosphate) [1]. This ultimately results in an influx of calcium via opening of voltage-dependent calcium-ion channels, and the subsequent binding of calcium ions to calmodulin triggers the exocytosis of insulin-containing secretory granules. The central issue of this presentation is the fact that the occurrence of K_{ATP}-channels is not restricted to the pancreatic beta cells. These particular ion channels occur in several organ systems, including the cardiovascular system [2, 3].

The open state probability of K_{ATP}-channels is dependent on the cytosolic concentration of ATP. During hypoxia and/or ischaemia, the cytosolic concentration of ATP falls which directly results in opening of K_{ATP}-channels. The subsequent efflux of potassium induces hyperpolarization of the cell membrane which shortens the action potential in the myocardial cell leading to a reduction in the contractile amplitude of myocardial cells. In vascular smooth muscle cells, opening of K_{ATP}-channels and subsequent hyperpolarization exerts relaxation of these cells, resulting in an obvious vasodilator response.

The vascular smooth muscle cell K_{ATP}-channels can be opened pharmacologically by potassium-channel-opening drugs such as cromakalim and the classical vasodilator drug diazoxide [3]. Glibenclamide is able to reduce the vasodilator response to these K_{ATP} channel-opening drugs, indicating the ability to block vascular K_{ATP}-channels. Apart from the interaction with K_{ATP}-channel-opening drugs, glibenclamide has also been reported to inhibit the vasodilator response to adenosine, and to (endothelium-dependent) vasodilators such as acetylcholine, vasoactive intestinal peptide and insulin [4]. Also in the myocardial cell, glibenclamide is able to reduce the response to K_{ATP}-channel-opening agents [4].

Animal experiments have shown that the ischaemia-induced opening of myocardial K_{ATP}-channels is an endogenous cardioprotective mechanism against ischaemia and reperfusion damage. In several ischaemia models glibenclamide increased infarct size [5, 6]. On the other hand blockade of the sulphonylurea receptor is associated with a reduction in ischaemia-related arrhythmias [4]. Not only myocardial K_{ATP}-channels are involved in the response to ischaemia. Other investigators have demonstrated that the vascular smooth muscle cell response to ischaemia is also inhibited by sulphonylurea derivatives, represented by a reduction of the post-occlusive hyperaemic response after pretreatment with glibenclamide.

Interestingly, the newly developed sulphonylurea derivative glimepiride seems to act more selectively, since its hypoglycaemic action is more pronounced than that of glibenclamide, whereas animal data suggest the absence of interaction with vascular K_{ATP}-channels [4].

Experimental data in humans

For several reasons the conclusions from animal experiments are not necessarily relevant to the clinical situation for treatment of non-insulin-dependent diabetes (NIDDM) by daily glibenclamide ingestion: 1) the sulphonylurea concentrations used in most animal studies are much higher than those reached during the treatment of NIDDM; 2) in human in vivo

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conditions, glibenclamide is highly protein bound which considerably reduces the free drug concentration; 3) there are large differences between species, and therefore the principles of interaction between glibenclamide and cardiovascular K_{ATP}-channels are not necessarily relevant to the human situation; and 4) the majority of the experiments show an acute interaction between sulphonylurea derivatives and cardiovascular K_{ATP}-channels, but this may not be relevant to the chronic setting of NIDDM treatment.

Up to now, human data on this issue are scarce. Kosmas et al. [7] recently showed a reduced post-ischaemic vasodilation after the oral administration of glibenclamide. We recently reported the effects of glibenclamide and tolbutamide on vascular K_{ATP}-channels in humans [8–10]. In that study, the perfused forearm technique was used. The interaction with vascular K_{ATP}-channels was studied by investigating the interaction with diazoxide. Therefore, diazoxide was used as a pharmacological tool to open vascular K_{ATP}-channels. In these studies we showed that glibenclamide was able to attenuate diazoxide-induced and also ischaemia-induced vasodilation. Since the systemic glibenclamide concentrations remained low, our data were not confounded by metabolic effects such as hyperinsulinaemia or hypoglycaemia. Apparently, the perfused forearm technique with infusions of diazoxide as a K_{ATP}-channel-opener appeared to be an appropriate human in vivo model to quantify the K_{ATP}-channel-blocking properties of sulphonylurea derivatives at the level of the vascular wall. Therefore, we also tested the newly developed sulphonylurea derivative glimepiride, that has been reported to be devoid of interactions with vascular K_{ATP}-channels in an animal model. Indeed, when we infused glimepiride into the brachial artery, diazoxide responses were not inhibited. Apparently, pancreatic and vascular K_{ATP}-channels have different characteristics in humans, which agrees with recent molecular biological observations [8]. Finally, experiments in patients with coronary artery disease have shown that ischaemic preconditioning is inhibited 1 h after the ingestion of 10 mg of glibenclamide [11]. This, as well as the antiarrhythmic properties of glibenclamide in ischaemic conditions, argues for an interaction between glibenclamide and myocardial K_{ATP}-channels.

Although the aforementioned data point towards a significant interaction between sulphonylurea derivatives and vascular K_{ATP}-channels, the clinical relevance of these observations remains unclear. It is obvious that results from clinical trials with well defined end points, like for example the United Kingdom Prospective Diabetes Study (UKPDS), are needed to elucidate this interesting issue.

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