Review

Insulin secretion and its modulation by antiarrhythmic and sulfonylurea drugs

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Received 7 October 1996; accepted 24 December 1996

Abstract

Cardiovascular drugs such as antiarrhythmic agents with Vaughan Williams class Ia action have been found to induce a sporadic hypoglycemia. Recent investigation has revealed that these drugs induce insulin secretion from pancreatic β-cells by inhibiting ATP-sensitive K+ (K_ATP) channels in a manner similar to sulfonylurea drugs. The mechanism underlying block of K_ATP channels by antiarrhythmic drugs was different, however, from that of sulfonylureas: firstly, because binding of radioactive glibenclamide could not be inhibited by unlabelled antiarrhythmic agents, and vice versa; secondly, because the two compounds differ in the kinetics and sidedness of drug action—antiarrhythmic drugs act on the channel from the inner surface of the cell membrane, whereas glibenclamide binds through the intramembrane pathway; finally, it was shown that functional K_ATP channels in β-cells are composed of two distinct molecules—a sulfonylurea receptor (SUR) and a channel pore-forming subunit, an inwardly-rectifying K channel with two transmembrane regions (Kir6.2). Antiarrhythmic drugs reversibly inhibit the K+ conductance displayed by the Kir6.1 (a putative K_ATP channel clone)-transfected NIH3T3 cells. Therefore they appear to interact directly with the pore-forming subunit, thereby inhibiting K_ATP channel currents and exerting an insulinotropic effect.

Keywords: Antiarrhythmic drugs; Sulfonylureas; Potassium channel, ATP-sensitive

1. Introduction

One of the undesired and peculiar side-effects of antiarrhythmic agents with Vaughan Williams class Ia action such as disopyramide and cibenzoline is that of sporadic hypoglycemia [1–8]. During antimalarial treatment with quinine, an optical isomer of quinidine (prototype of Vaughan Williams class Ia antiarrhythmics), severe hypoglycemic attacks have been reported [9,10]. Quinine has been shown to block pancreatic ATP-sensitive K+ (K_ATP) channels [11,12]. In some previous reports, an increased level of immunoreactive insulin (IRI) was associated with drug-induced hypoglycemia. The findings suggested that the compounds accelerate insulin secretion and thereby induce hypoglycemia. More recently, by applying patch-clamp techniques to pancreatic β-cells along with receptor-binding assays and IRI measurements, they were found to reversibly inhibit pancreatic K_ATP channels and promote insulin release, irrespective of blood sugar level [13–16]. In this brief review, we would like to summarize recent progress in the research of insulin secretion and its modulation by antiarrhythmic and sulfonylurea drugs.

2. The pancreatic K_ATP channel is involved in the glucose-sensor system and regulates insulin-secreting level

Although the K_ATP channel was first identified in cardiac myocytes [17], its physiological role as a metabo-
Fig. 1. A schematic representation of the mechanism of insulin secretion from pancreatic the β-cell. GLUT2 = glucose transporter isoform 2; Kir6.2 = K channel pore-forming subunit with two transmembrane domains; SU = sulfonylurea compounds; SUR = sulfonylurea receptor.

3. The K\textsubscript{ATP} channel is distinct from the sulfonylurea receptor

Direct proof that sulfonylurea drugs inhibit β-cell K\textsubscript{ATP} channels [26,27] was made soon after the discovery of the channels by patch-clamp experiments [18,19]. The sulfonylurea receptor (SUR) has since been assumed to be the K\textsubscript{ATP} channel, a target for molecular cloning. In 1995, Aguilar-Bryan et al. [28] obtained a cDNA encoding SUR. The putative protein structure shows 13 transmembrane segments and two ATP-binding sites, indicating that it is a member of the ATP-binding cassette (ABC) transporter superfamily. However, SUR alone was unable to reconstitute K\textsubscript{ATP} channel activity in a mammalian cell line [28]. This contrasts with the finding that Cl\textsuperscript{−} channel activity can be reconstituted in NIH3T3 cells by the expression of epithelial cystic fibrosis transmembrane conductance regulator (CFTR) mRNA, another member of the ABC superfamily [29].

In the same year, Inagaki et al. [30] showed that the functional K\textsubscript{ATP} channels in β-cells are composed of two distinct molecules: SUR and Kir6.2. The latter is an inwardly rectifying K\textsuperscript{+} channel, with two membrane-spanning regions, obtained by means of homology cloning from a mouse insulinoma cell line with Kir6.1 [31] as a probe. Kir6.2 turned out to serve as the pore-forming subunit. When COS-1 cells were transfected with either Kir6.2 or SUR alone, no channel activity was seen. However, co-expression of SUR and Kir6.2 could display the activity of a K\textsuperscript{+} channel compatible with native K\textsubscript{ATP} channels [30]. Thus, SUR conferred both ATP and sulfonylurea drug sensitivity on Kir6.2, thereby forming the functional K\textsubscript{ATP} channel. In contrast, Kir6.1 (or uKir6.1 [31]) was a ubiquitous type of K\textsubscript{ATP} channel cloned from a rat pancreatic islet cDNA library and shares ~70% homology with Kir6.2. Unlike Kir6.2, Kir6.1 transfection with HEK 293 cells alone displayed the channel activity. However, when co-transfected with SUR, Kir6.1 obtained sensitivity to ATP and sulfonylurea [32,33].

4. Class Ia antiarrhythmic agents have insulinotropic action by inhibiting pancreatic K\textsubscript{ATP} channels

Similar to sulfonylurea drugs, class Ia antiarrhythmics have a dose-dependent insulinotropic action by inhibiting pancreatic K\textsubscript{ATP} channels [13–16]. Disopyramide and cibenzoline have been found to have high EC\textsubscript{50} values, thus increasing IRI from rat pancreatic islets (23.3 μM [14] and 94.2 μM [16], respectively). However, it has been reported that IRI was increased by as low as 6 μM of cibenzoline although the dose–response relation was not available in the report [34]. Assuming that these relatively high values are the same in humans, it is compatible with the clinical observation that hypoglycemia associated with these compounds occurs quite infrequently since therapeutic concentrations are reported to be ~1 μM [35].

During the patch-clamp experiment using isolated β-cells from rats, however, the IC\textsubscript{50} values for blocking K\textsubscript{ATP} channels from outside the β-cell membrane were lower than the concentrations needed to induce insulin release (11 μM [14] for disopyramide and 5.2 μM [16] for cibenzoline). In the cell-attached mode, alkalinization of extracellular medium containing cibenzoline increased its inhibitory action. The IC\textsubscript{50} was reduced from 26.8 μM at pH 6.2 to 0.9 μM at pH 8.4. In the inside-out mode, where the drug can get access to the binding site from the cytoplasmic side of the membrane, the compounds were
more potent (IC₅₀ = 3.6 μM [14] for disopyramide and 0.4 μM for cibenzoline [16]) and their blocking kinetics rapid in onset.

The activities of K_ATP channels are known to be regulated by intracellular ligands: ATP-dependent closure of the channel was re-opened by micromolar amounts of ADP [36,37]. In rat β-cells, ADP (100 μM) was found to recover cibenzoline (10 μM)-, but not glibenclamide (1 μM)-induced block of channel activity [16]. These experimental results suggest that antiarrhythmic agents bind from the cytoplasmic side of the cell membrane (Fig. 1). This contrasts with the case of glibenclamide which has been assumed to act via an intramembrane pathway [38,39] (Fig. 1).

5. The binding site of antiarrhythmic agents is distinct from SUR

The cibenzoline block was enhanced by alkalinization [16]. Since the pKa value for cibenzoline is 10.6, a 10-fold change of alkalinization (at pH < 10.6) produces a 10-fold higher concentration of the uncharged (non-ionized) form of the compound, which can more easily permeate the cell membrane than the charged form [40]. The drug thus appeared to reach the binding site on the inner side via a membrane pathway. In the receptor-binding assay (Fig. 2), we found that the binding of [³²P]glibenclamide to pancreatic islets was inhibited by glibenclamide but not by cibenzoline. In contrast, [³²P]cibenzoline binding was displaced by unlabelled cibenzoline but not by glibenclamide [16].

During the whole-cell mode of patch-clamp experiments using Kir6.1-transfected NIH3T3 cells, we found that these antiarrhythmic agents reversibly blocked the K⁺ conductance carried by Kir6.1 channels (IC₅₀ for cibenzoline is ~12 μM, Fig. 2B). Glibenclamide, however, was unable to affect the conductance (data not shown). These lines of experimental results suggest that the binding site for antiarrhythmic drugs is distinct from SUR [29], but is probably the channel pore itself (Kir6.2).

6. Clinical implications

According to the clinical literature [1–8], antiarrhythmic-drug-induced hypoglycemia appears to be associated with hypoalbuminemia, renal insufficiency or diabetes mellitus, especially in elderly patients. Therefore, special care should be paid to elderly diabetic patients who are already receiving sulfonylureas because renal dysfunction is one of the most common complications in this cohort of patients. The insulinotropic effect of antiarrhythmic agents may be additional to the action of sulfonylurea drugs because these compounds act in a different manner through distinct receptors.
Acknowledgements

The work from our laboratories presented here was partly supported by Grants-in-Aid for Priority Areas of 'Channel-Transporter Correlation' from the Japan Ministry of Education, Science and Culture.

References