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European Journal of Pharmacology 381 (1999) 71–76

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Troglitazone but not pioglitazone affects ATP-sensitive K^+ channel activity

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Received 12 April 1999; received in revised form 19 July 1999; accepted 27 July 1999

Abstract

We compared the effects of the two thiazolidinedione derivatives, troglitazone and pioglitazone, on ATP-sensitive K^+ (K_{ATP}) channel activities. Pancreatic β-cell type and cardiac type K_{ATP} channels were reconstituted in COS-1 cells (SV 40-transformed African green monkey kidney (AGMK) cells) by heterologously expressing sulfonylurea receptor 1 (SUR1) plus Kir6.2 and sulfonylurea receptor 2A (SUR2A) plus Kir6.2, respectively. Troglitazone inhibited [$^{86}Rb^+$] efflux in both K_{ATP} channel types in the presence of metabolic inhibitors, which was confirmed by electrophysiological techniques. The [$^{86}Rb^+$] efflux increased by the channel openers diazoxide and pinacidil was abolished by troglitazone. In contrast, pioglitazone did not affect these channel activities in either type K_{ATP} channel. These results suggest that troglitazone modulates the various cellular functions including insulin secretion by inhibiting the K_{ATP} channels, while pioglitazone has no effect on K_{ATP} channel activity.

Keywords: K^+ (K_{ATP}) channel, ATP-sensitive; Sulfonylurea receptor; Troglitazone; Pioglitazone

1. Introduction

ATP-sensitive K^+ channels (K_{ATP} channels) are characterized by an inhibition of channel opening when the ATP/ADP ratio at the cytoplasmic cell surface is increased (Noma, 1983). K_{ATP} channels play an important role in various cellular responses such as secretion and muscle contraction, by linking the metabolic status of the cell to its membrane potential (Ashcroft, 1988); they have been found in various tissues including pancreatic β-cells, skeletal muscle, brain, and vascular and nonvascular smooth muscle (Cook and Hales, 1984; Spruce et al., 1985; Ashford et al., 1988; Standen et al., 1989). Since the discovery of K_{ATP} channels in pancreatic β-cells, the sulfonylureas, insulin secretagogues widely used as oral hypoglycemic agents in the treatment of diabetes mellitus, have been shown to inhibit the activity of these K_{ATP} channels (Sturgess et al., 1985; Trube et al., 1986). Molecular cloning of the high affinity sulfonylurea receptor (SUR) revealed it to be a member of the ATP-binding cassette (ABC) superfamily (Aguilar-Bryan et al., 1995). It has been shown that classical K_{ATP} channels are complexes of two subunits, Kir6.2 subunits, which form the K^+-selective ion channel pore, and SUR subunits, receptors for sulfonylureas (Seino, 1999); pancreatic β-cell type and cardiac type K_{ATP} channels comprise Kir6.2 and SUR1 subunits (Inagaki et al., 1995; Sakura et al., 1995) and Kir6.2 and SUR2A (Inagaki et al., 1996) subunits, respectively. The thiazolidinedione derivatives troglitazone and pioglitazone are recently developed orally active hypoglycemic compounds that improve insulin resistance in diabetic rodents and in patients with diabetes mellitus (Kobayashi et al., 1982; Fujiwara et al., 1988, 1991; Ciaraldi et al., 1990; Hofmann et al., 1992; Kemnitz et al., 1994). We have previously shown that troglitazone is capable of directly stimulating insulin secretion from pan-

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0014-2999/99/$ - see front matter
PII: S0014-2999(99)00539-7

creatic β-cells, although it is not apparent until after a few minutes (Masuda et al., 1995). In this study, we compare the effects of trogliatizone and piogliatazone on reconstituted pancreatic β-cell type and cardiac type K_{ATP} channels, and find that while troglitazone has an effect, pioglitazone has none, suggesting the different effects of these two anti-diabetic agents.

2. Materials and methods

2.1. Cell culture and transfection

COS-1 cells (SV 40-transformed African green monkey kidney (AGMK) cells) were plated at a density of 2×10^5 cells per dish (35 mm in diameter) for single channel analysis or 3×10^5 per well (30 mm 6-well dish) for [$^{86}Rb^+$] efflux measurements, and cultured in Dulbecco's modified Eagles medium (DMEM, 4500 mg/l glucose) supplemented with 10% fetal calf serum. For single channel analysis, cytomegalovirus-promoter-driven hamster SUR1-expression plasmid, pCMVhaSUR1 (1.5 μg), or rat SUR2A-expression plasmid, pCMVrSUR2A (1.5 μg) and mouse Kir6.2-expression plasmid, pCMVmKir6.2 (1.5 μg), with the expression plasmid for green fluorescence protein (pSRαGFP, 0.05 μg) as a reporter gene (Marshall et al., 1995), were transfected into COS-1 cells with Lipofectoamine and OPTI-MEM I reagents (Life Technologies) and pAdVantage (0.5 μg, Promega), according to the instructions of the manufacturer. For [$^{86}Rb^+$] efflux measurements, pCMVhaSUR1 (1.0 μg) or pCMVrSUR2A (1.0 mg) and pCMVmKir6.2 (1.0 μg) were transfected into COS-1 cells with Lipofectoamine and OPTI-MEM I reagents.

2.2. [$^{86}Rb^+$] efflux measurements

Two days after transfection, [^{86}Rb]Cl (1 mCi/ml, Amersham Pharmacia Biotech, UK) was added in fresh DMEM containing 10% fetal calf serum and incubated for 12–24 h. The cells were further incubated for 30 min at 37°C in Krebs–Ringer solution (118 mM NaCl, 5.0 mM $NaHCO_3$, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_2$, 20 mM HEPES, pH 7.4) containing 1 mCi/ml [^{86}Rb]Cl with or without 2.5 mg/ml of oligomycin and 1 mM of 2-deoxy-D-glucose. After washing the cells once in [$^{86}Rb^+$]-free Krebs–Ringer solution, with or without added metabolic inhibitors and thiazolidinedione derivatives, [$^{86}Rb^+$] efflux was measured at 37°C as previously described (Inagaki et al., 1995): briefly, the medium was removed at each time point and replaced with fresh medium containing the indicated concentrations of troglitazone or pioglitazone, with or without metabolic inhibitors. The medium at each time point was counted, and the values were summed to determine flux. The data are presented as the percentage of total cellular [$^{86}Rb^+$]. All of the curves are the average of three or more independent experiments. Troglitazone and pioglitazone were dissolved in dimetylsulfoxide (DMSO) at a concentration of 100 mM.

2.3. Electrophysiology

After transfection, the cells were cultured for 48 to 72 h before recordings. The transfected cells were selected by

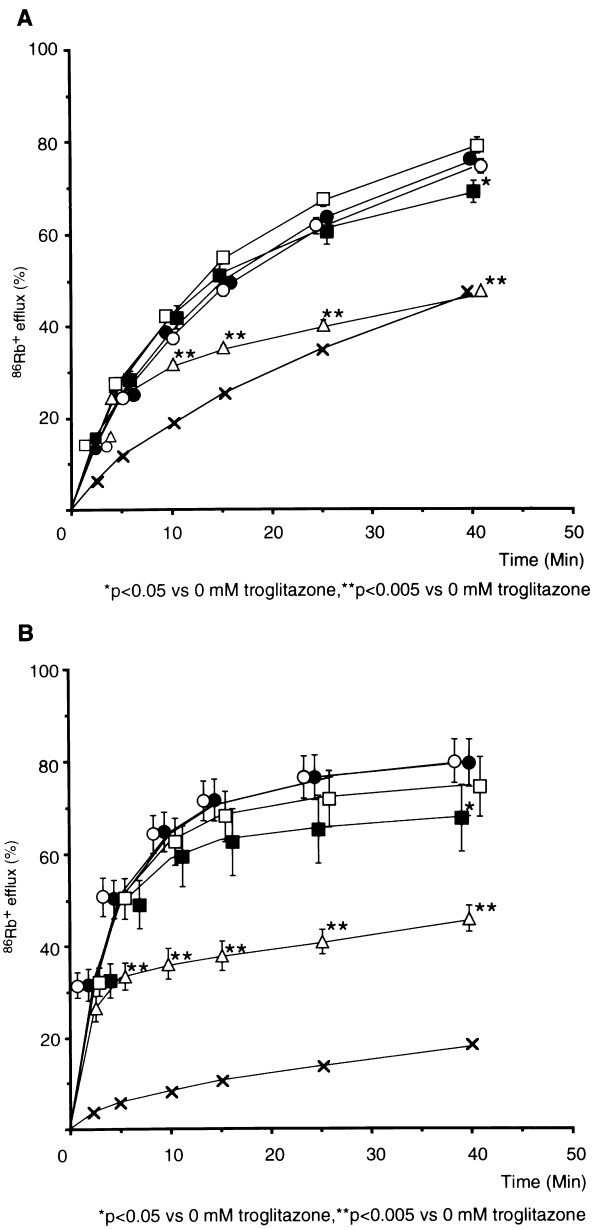

Fig. 1. The effect of troglitazone on [$^{86}Rb^+$] efflux from COS-1 cells coexpressing SUR1 and Kir6.2. Basal efflux from COS-1 cells transfected pCMV6c alone (crosses) and SUR1 plus Kir6.2 (open circles) in the absence (A) or presence (B) of metabolic inhibitors. The cells expressing K_{ATP} channels were incubated with 1 μM (closed circles), 3 μM (open squares), 10 μM (closed squares) and 30 μM (open triangles) troglitazone. Since the data points are tightly clustered, the symbols have been offset ±1 or 2 min for clarity.

green fluorescence under a microscope (Marshall et al., 1995). Single channel recordings were made in the excised inside-out patch configurations as described (Hamill and Sakmann, 1981; Inagaki et al., 1995). The bath solution contained 110 mM potassium aspartate, 30 mM KCl, 2 mM $MgSO_4$, 1 mM EGTA, 0.084 mM $CaCl_2$ and 10 mM MOPS (pH 7.2). Dipotassium ATP (0.001 mM) was added to the bath solution unless otherwise noted. The pipette solution contained 140 mM KCl, 2 mM $CaCl_2$ and 5 mM MOPS (pH 7.4). Troglitazone and pioglitazone were dissolved in DMSO at a concentration of 300 mM, and then suspended in the bath solution before use. Recordings were made at 20°C–22°C.

3. Results

The [$^{86}Rb^+$] efflux from COS-1 cells cotransfected with SUR1 and Kir6.2 is greater than the efflux from those transfected with vector alone in the absence or presence of metabolic inhibitors, indicating that the efflux represents the activity of the K_{ATP} channels (Fig. 1). Troglitazone had an inhibitory effect on [$^{86}Rb^+$] efflux from COS-1 cells cotransfected with SUR1 and Kir6.2. K_{ATP} channel activity was decreased by 30 and 100 μM (data not shown) troglitazone, in the absence (Fig. 1A) or presence (Fig. 1B) of metabolic inhibitors.

The [$^{86}Rb^+$] efflux from COS-1 cells cotransfected with SUR2A and Kir6.2 is greater than that from sham transfected COS-1 cells only in the presence of metabolic inhibitors, showing that SUR2A/Kir6.2 channels are closed in their absence in COS-1 cells. The effect of troglitazone was, therefore, examined on [$^{86}Rb^+$] efflux from COS-1 cells cotransfected with SUR2A and Kir6.2 in the presence of metabolic inhibitors. [$^{86}Rb^+$] efflux through the reconstituted SUR2A/Kir6.2 channels was inhibited by as little as 3 μM of troglitazone (Fig. 2).

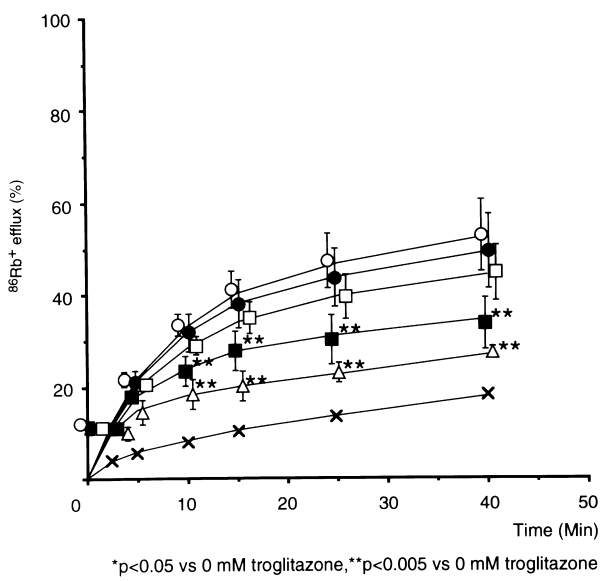

Fig. 2. The effect of troglitazone on [$^{86}Rb^+$] efflux from COS-1 cells coexpressing SUR2A and Kir6.2. Basal efflux from COS-1 cells transfected pCMV6c alone (crosses) and SUR2A plus Kir6.2 (open circles) in the presence of metabolic inhibitors. The cells expressing K_{ATP} channels were incubated with 1 μM (closed circles), 3 μM (open squares), 10 μM (closed squares) and 30 μM (open triangles) troglitazone. Since the data points are tightly clustered, the symbols have been offset ±1 or 2 min for clarity.

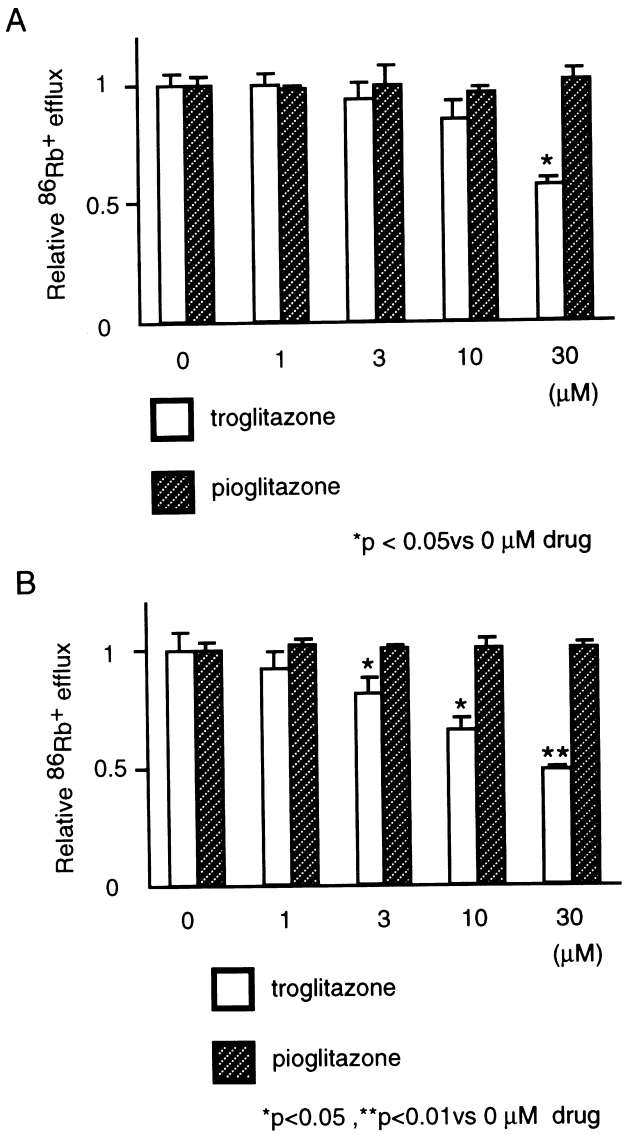

Fig. 3. The effects of troglitazone and pioglitazone on K_{ATP} channels reconstituted from SUR1 plus Kir6.2 or SUR2A plus Kir6.2. (A, B). Relative values of [$^{86}Rb^+$] efflux for 40 min from COS-1 cells coexpressing SUR1 plus Kir6.2 (A) and SUR2A plus Kir6.2 (B) with the indicated concentrations of troglitazone (open columns) or pioglitazone (closed columns) in the presence of metabolic inhibitors. Values are expressed as means ± S.E.M., relative to the [$^{86}Rb^+$] efflux from COS-1 cells without troglitazone or pioglitazone.

Pioglitazone did not affect [$^{86}Rb^+$] efflux through K_{ATP} channels of either the pancreatic β-cell type or the cardiac type (Fig. 3).

Pancreatic β-cell type and cardiac type K_{ATP} channel activities are inhibited by glibenclamide. A total of 10 or

30 μM troglitazone augmented the submaximal inhibitory effects of 3 nM or 1 μM glibenclamide on pancreatic β-cell type and cardiac type K_{ATP} channels, respectively (Fig. 4). In addition, troglitazone (10 or 30 μM) abolished the stimulatory effects of diazoxide (200 μM) and pinacidil (200 μM) on pancreatic β-cell type and cardiac type K_{ATP} channels, respectively (Fig. 5).

Troglitazone inhibited activity of K_{ATP} channels reconstituted from SUR1 and Kir6.2 at concentrations of 30, 100 (data not shown), and 300 μM (Fig. 6A). Single channel conductance was not affected by the troglitazone

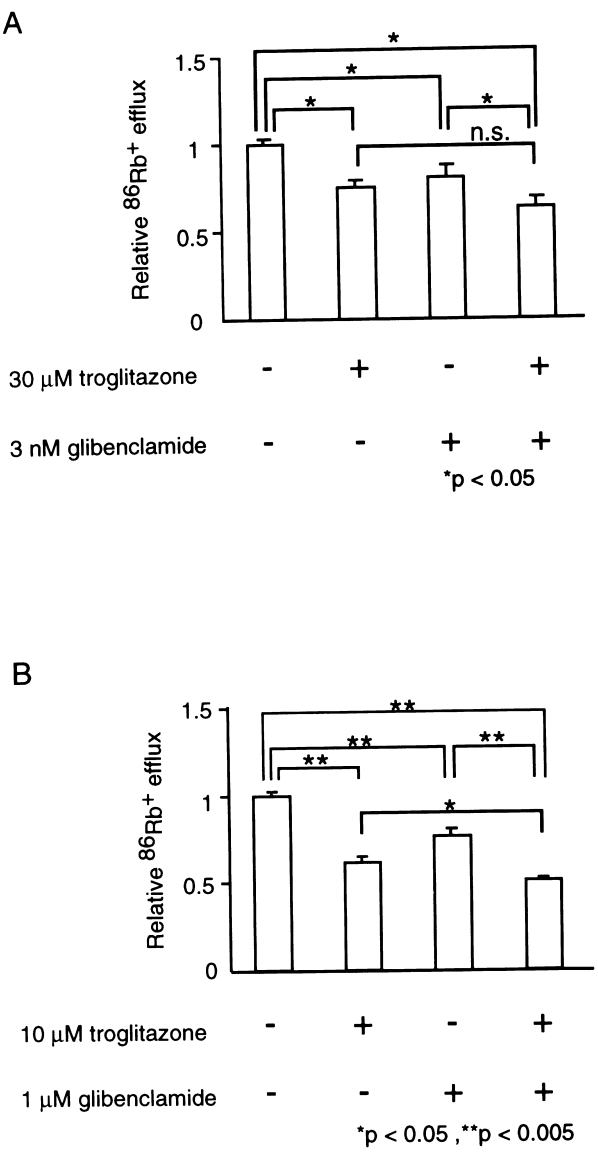

Fig. 4. The effect of troglitazone on K_{ATP} channels partially inhibited by glibenclamide. (A, B) Relative values of [$^{86}Rb^+$] efflux for 40 min from COS-1 cells coexpressing SUR1 plus Kir6.2 (A) and SUR2A plus Kir6.2 (B) with or without the indicated concentrations of troglitazone (A, 30 μM; B, 10 μM) and glibenclamide (A, 3 nM; B, 1 μM) in the presence of metabolic inhibitors. Data are given as means ± S.E.M., relative to the [$^{86}Rb^+$] efflux from COS-1 cells without troglitazone and glibenclamide.

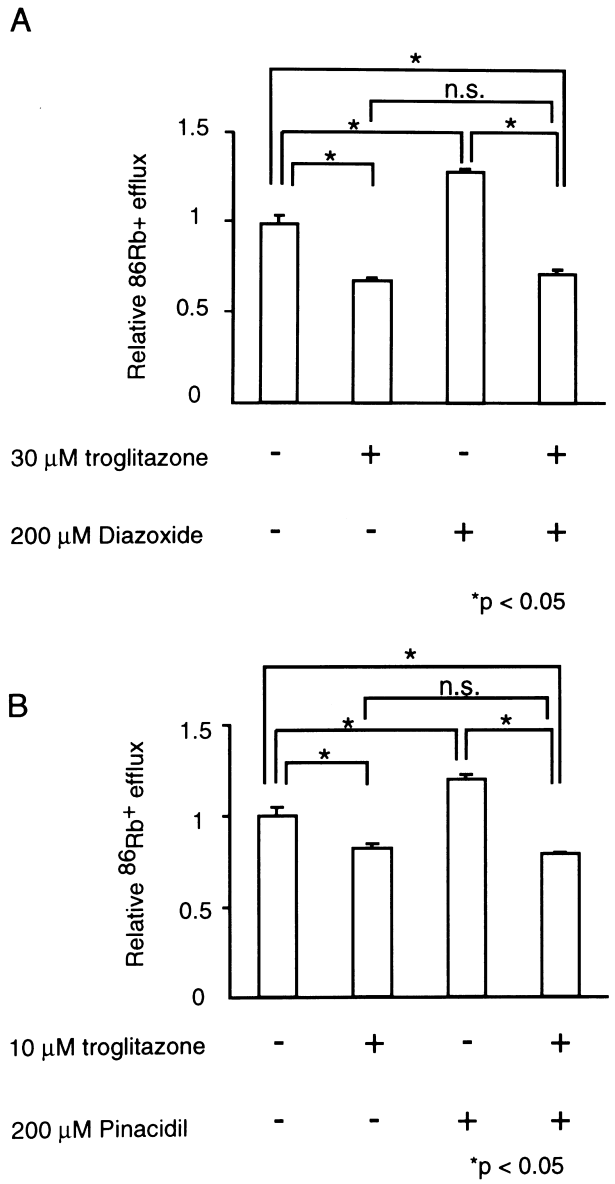

Fig. 5. The effect of troglitazone on K_{ATP} channels activated by K_{ATP} channel openers. (A, B) Relative values of [$^{86}Rb^+$] efflux for 40 min from COS-1 cells coexpressing SUR1 plus Kir6.2 (A) and SUR2A plus Kir6.2 (B) with or without the indicated concentrations of troglitazone (A, 30 μM; B, 10 μM) and the K_{ATP} channel opener diazoxide (A, 200 μM) or pinacidil (B, 200 μM) in the absence of metabolic inhibitors. Data are given as means ± S.E.M., relative to the [$^{86}Rb^+$] efflux from COS-1 cells without troglitazone and K_{ATP} channel openers.

application (Fig. 6A). The inhibitory effect of 30 μM troglitazone was abolished soon after washout of the drug (Fig. 6A-a). Extensive washout of the drug was required for full recovery of channel activity after application of 300 μM troglitazone (Fig. 6A-b). Similarly, troglitazone inhibited activity of K_{ATP} channels reconstituted from SUR2A and Kir6.2 at concentrations higher than 100 μM (Fig. 6B). In contrast to the effect of troglitazone, pioglitazone did not inhibit K_{ATP} channel activity at concentrations up to 300 μM in COS-1 cells transfected with either

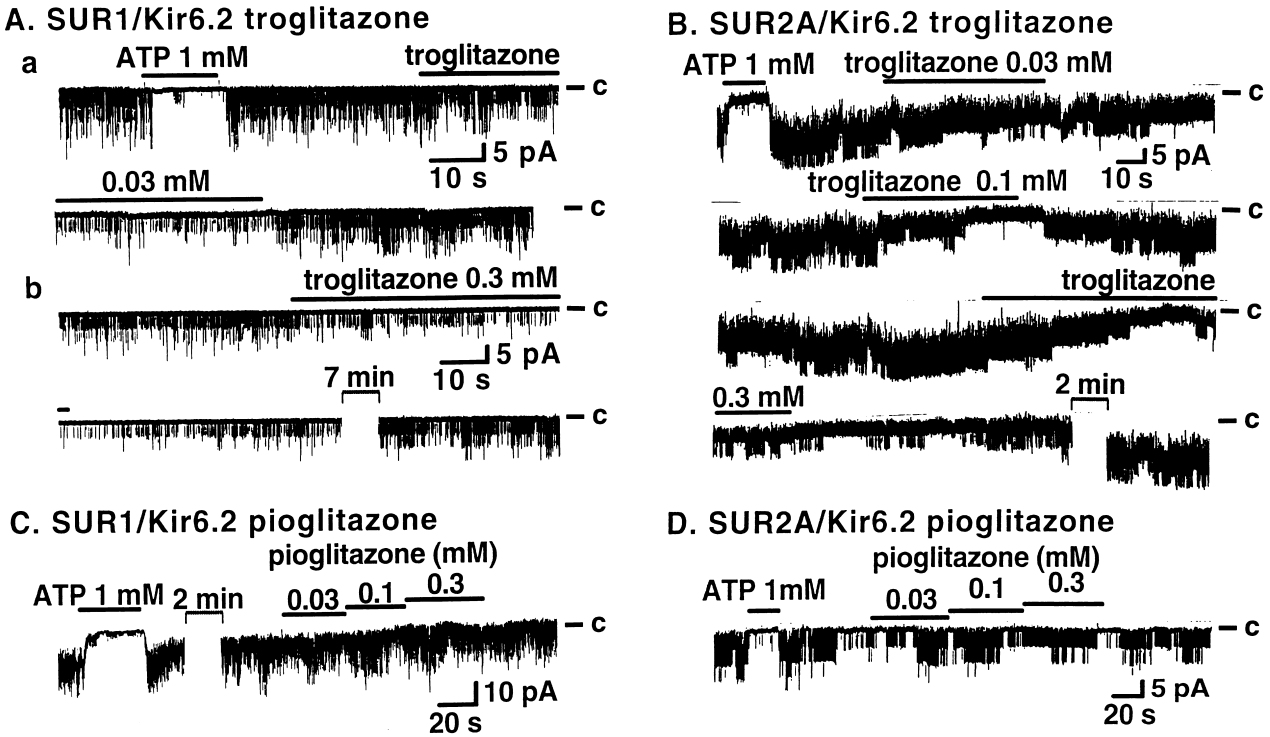

Fig. 6. Electrophysiological recordings from COS-1 cells expressing reconstituted K_{ATP} channels. (A, B) The effects of troglitazone on K_{ATP} channel currents in COS-1 cells expressing SUR1 plus Kir6.2 (A) or SUR2A plus Kir6.2 (B). Troglitazone inhibits SUR1/Kir6.2 channel currents reversibly at a concentration of 30 μM (a) or 300 μM (b). (B) Troglitazone inhibits SUR2A/Kir6.2 channel currents at concentrations of 100 and 300 μM. (C and D) (C, D) The effect of pioglitazone on K_{ATP} channel currents in COS-1 cells expressing SUR1 plus Kir6.2 (C) or SUR2A plus Kir6.2 (D). Pioglitazone shows no apparent inhibitory effect on these channels. The recordings were made in the inside-out configuration of patch–clamp technique. The horizontal bars and numbers indicate application periods and concentration of ATP, troglitazone and pioglitazone. Calibrations are shown in each panel. The state in which all the channels are closed is represented by the symbol C.

SUR1 plus Kir6.2 (Fig. 6C) or SUR2A plus Kir6.2 (Fig. 6D).

4. Discussion

We have previously reported that troglitazone stimulates insulin secretion from pancreatic islet (Masuda et al., 1995). In this study, we show that the insulinotropic effect of troglitazone, at least in part, may be inhibition of pancreatic β-cell type K_{ATP} channels. [$^{86}Rb^{+}$] efflux and electrophysiological characterization using COS-1 cells heterologously expressing SUR1 plus Kir6.2 and SUR2A plus Kir6.2 shows that troglitazone but not pioglitazone inhibits the activity of both types of K_{ATP} channel. These results are consistent with reports that troglitazone inhibits channel activity in Cambridge rat insulinoma-G1 (CRI-G1) insulin-secreting cells (Lee et al., 1996) and in neurons in the ventromedial hypothalamus (Lee and Boden, 1997). The initial examination of pancreatic β-cell type K_{ATP} channel activity in the presence of troglitazone failed to show its inhibitory effect, although troglitazone has a putative non-competitive binding site at the SUR (Masuda et al., 1995).

The thiazolidinedione derivatives have been shown to bind at the ligand-binding domain of the peroxisomal proliferator-activated receptor-gamma (PPARγ) (Berger et al., 1996; Forman et al., 1995), so it seems unlikely that activation of PPARγ should be followed by inhibition of K_{ATP} channel activity, since pioglitazone, another thiazolidinedione derivative also activates PPARγ. Recently, Ohtani et al. reported that pioglitazone stimulates insulin secretion in hamster β-cell line (HIT-T15) by inducing Ca^{2+} influx (Ohtani et al., 1996). Taken together, these data suggest that the thiazolidinedione derivatives could have several target proteins including the K_{ATP} channels in pancreatic β-cells.

In heart and skeletal muscle, the opening of the K_{ATP} channels has been implicated in the shortening of the action potential duration and the cellular loss of K^{+} during ischemia, hypoxia, and other metabolic insults, and leads to cytoprotection and vascular dilatation (Terzic et al., 1995). The inhibitory effects of troglitazone on K_{ATP} channel activity, therefore, could adversely affect patients during cardiac ischemia or exercise which causes a reduction of ATP in cardiac and skeletal muscles.

Acknowledgements

We thank J. Bryan for providing us with hamster SUR1 cDNA clone. This study was supported by Grants-in-Aid

from the Ministry of Education, Science, Sports, and Culture and by the grants from the Ministry of Health and Welfare, Japan; Takeda Life Science; The Sumitomo Foundation; Suzuken Memorial Foundation; and Kowa Life Science Foundation. We are grateful to Sankyo Company, Tokyo, Japan and Takeda Chemical Industry, Osaka, Japan, for supplying troglitazone and pioglitazone, respectively.

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