Biochemical and Biophysical Research Communications 460 (2015) 850–856

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

P2Y purinergic receptor-regulated insulin secretion is mediated by a cAMP/Epac/Kv channel pathway

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ARTICLE INFO

Article history:
Received 19 March 2015
Available online 1 April 2015

Keywords:
P2Y purinergic receptor
Insulin secretion
Cyclic AMP
Voltage-dependent potassium channels
Diabetes

ABSTRACT

Enhancement of insulin secretion is a major therapeutic approach for type 2 diabetes (T2D). Activation of P2Y purinergic receptor (P2YR) causes potentiation of insulin secretion in a glucose-dependent manner, making it a promising therapeutic target for T2D. Here we show that activation of P2YR to potentiate insulin secretion is mediated by adenylyl cyclase/cyclic AMP (cAMP) and the downstream effector, exchange protein directly activated by cAMP (Epac), leading to inhibition of voltage-dependent potassium (Kv) channels. P2YR-mediated Kv channel inhibition results in prolongation of action potential duration, and in turn elevates intracellular Ca^{2+} level and insulin secretion. Taken together, the data indicate that cAMP/Epac/Kv channel pathway mediates P2YR-regulated insulin secretion, which may have important therapeutic implications for T2D.

1. Introduction

Type 2 diabetes (T2D) is characterized by relatively reduced insulin secretion and/or insulin resistance. Thus, enhancement of insulin secretion is a major approach in the treatment of T2D. In pancreatic islets of human and other species [1,2], activation of P2Y purinergic receptor (P2YR) has been shown to stimulate insulin secretion in a glucose-dependent manner, which is of specific interest when considering P2YR as a promising therapeutic target for T2D treatment [3]. However, the mechanism of P2YR-mediated insulin secretion is not fully understood.

Physiologically, pancreatic β cells secrete insulin via the glucose-sensing pathway, which is started by high glucose-induced closure of ATP-sensitive K^+ (K_{ATP}) channels, in the next step the resultant membrane depolarization activates voltage-dependent Ca^{2+} channels (VDCCs), leading to increase of intracellular Ca^{2+} ($[Ca^{2+}]_i$), and finally triggers exocytosis of insulin granules [4]. In this stimulus-secretion coupling processes, voltage-dependent potassium (Kv) channels have also been shown to be pivotal in regulating glucose-dependent insulin secretion. Studies demonstrate that Kv channels are involved in the repolarizing phase of the action potential in pancreatic β cells; and blockade of the Kv channel prolongs action potential duration (APD) and enhances insulin secretion [5,6].

In the current work, we show that activation of P2YR to potentiate insulin secretion is mediated by adenylyl cyclase (AC) and cyclic AMP (cAMP), and the cAMP downstream effector, exchange protein directly activated by cAMP (Epac), is a key signaling target for P2YR activation. We found that activation of P2YR inhibits Kv channels, and this effect is reversed by Epac inhibition, suggesting that Kv channels act downstream of Epac. We further show that K_V channels mediate P2YR activation-potentiated insulin secretion. Thus, in pancreatic β cells, AC/cAMP/Epac/Kv channel pathway may play a critical role in P2YR-mediated insulinotropic effect.

2. Materials and methods

2.1. Animals

Male SD rats (Animal Facility Center of Shanxi Medical University, China) were housed under a controlled temperature (23 ± 3 °C)

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http://dx.doi.org/10.1016/j.bbrc.2015.03.121
0006-291X/

and photoperiod (12 h-light/dark cycle). Rats weighing 180–250 g were used and received pellet-type food and tap water. The animal protocols were approved by the Animal Care and Use Committee of the Shanxi Medical University (Taiyuan, PR China).

2.2. Preparation of rat pancreatic islets and single islet cells

Islets were isolated from male SD rats by injection of collagenase P (Roche, Indianapolis, USA) at 1 mg/ml into the common bile duct. Pancreas was then separated and incubated at 37 °C for 11 min. After the density gradient centrifugation with histopaque-1077, islets were hand collected under a stereoscopic microscope. To obtain dispersed islet cells, pancreatic islets were dispersed into single cells by Dispase II digestion for 6 min. Intact islets or dispersed islet cells were cultured in Hyclone RPMI 1640 (Hyclone Beijing, China) medium containing 11.1 mM glucose supplemented with 10% fetal bovine serum, 0.004% β-mercaptoethanol, 100 U/ml penicillin and 100 μg/ml streptomycin, at 37 °C in an atmosphere of humidified air (95%) and CO_2 (5%) [7].

2.3. Measurements of insulin release from isolated islets

Each tube containing 5 islets was incubated for 0.5 h at 37 °C in Krebs–Ringer bicarbonate-HEPES(KRBH) buffer with 2.8 mM glucose as preincubation, followed by test incubation for 0.5 h at indicated glucose concentration in the presence or absence of ADPβS (Sigma–Aldrich, USA), Suramin (Millipore, USA), SQ 22536 (Cayman, USA), ESI-09 (Santa Cruz, USA), PKI (Santa Cruz, USA), TEA (Sigma–Aldrich, USA). The Krebs–Ringer bicarbonate-HEPES (KRBH) buffer contains (mM): 128.8 NaCl; 4.8 KCl; 1.2 KH_2PO_4; 1.2 $MgSO_4$; 2.5 $CaCl_2$; 5 $NaHCO_3$; 10 HEPES; and 2% BSA at pH 7.4. Then, the incubated supernatant was collected for insulin concentration measurement. The total insulin contents per tube of these islets lysed with 70% acid-ethanol solution (Ethanol/water/HCl (vol./vol.) = 150:47:3) were also measured. All values were normalized to total insulin content. The insulin secretion studies were carried out at 37 °C. Insulin concentrations were determined by Iodine [^{125}I] Insulin Radioimmunoassay Kit (North biological technology research institute of Beijing). The isolated islets were prepared from two to three SD rats in each experiment.

2.4. Measurements of $[Ca^{2+}]_i$

Pancreatic islet cells were cultured in 35 mm dishes and cultured in RPMI 1640 medium with 10% FBS for 24 h. The cells were then incubated by KRBH containing 5 μmlo/l Fluo 4-AM (Dojindo Laboratories, Japan) at 2.8 mM glucose for 30 min at 37 °C. The Fluo 4-AM was excitated at 494 nm and emission at 516 nm. $[Ca^{2+}]_i$ measurements were carried out using OLYMPUS FV1000 (Inverted microscope IX81) confocal microscope at room temperature. The cell fluorescence density (F0) change was plotted to represent the change in $[Ca^{2+}]_i$ levels.

2.5. Patch-clamp experiments

Rat pancreatic islet cells were cultured on glass coverslips in 35 mm dishes with RPMI 1640 medium before electrophysiological recordings. For electrophysiological recordings, coverslips were transferred to a recording chamber installed on an inverted microscope (Nikon Diaphot-TMD) and perfused with extracellular recording solution. The resistances of the patch pipettes is ranged from 4 to 7 MΩ when filled with pipette solution. Membrane currents, recorded using an EPC-10 amplifier and PULSE software from HEKA Electronik (Lambrecht, GER), were stored online in a computer. The β-cells were identified by cell capacitance (>4 pF). All experiments were proceeded at room temperature (22–25 °C).

For Kv current recording, β-cells were voltage-clamped at a holding potential of −70 mV and then shifted to the test potentials from −70 to 80 mV in 10 mV steps with pulses of 400 ms durations. The following intracellular solution was used: 140 mM KCl, 1 mM $MgCl_2$, 0.05 mM EGTA, 10 mM NaCl and 10 mM HEPES (pH 7.3 with KOH). The extracellular solution contained (mM): 141.9 NaCl, 5.6 KCl, 1.2 $MgCl_2$, 11.1 glucose, and 5 HEPES (pH 7.4 with NaOH).

As to the recordings of depolarization-evoked Ca^{2+} currents, we employed Ba^{2+} to replace Ca^{2+} as the charge carrier to amplify Ca^{2+} current responses during the depolarization stimulus. Here, β-Cells were voltage clamped at a holding potential of −70 mV and then shifted to the test potentials from −50 to 30 mV in 10 mV steps with the pulses of 50 ms duration. The following intracellular solution was used: 120 mM CsCl, 20 mM TEA, 1 mM $MgCl_2$, 0.05 mM EGTA, 10 mM HEPES, and 5 mM MgATP (pH 7.3 with CsOH). The extracellular solution contained: 100 mM NaCl, 20 mM TEA, 20 mM $BaCl_2$, 5 mM HEPES, 1 mM $MgCl_2$, 4 mM CsCl, and 3 mM glucose (pH 7.4 with NaOH).

Action potentials were recorded in the current-clamp mode by stimulating the cells with a 4 ms, 150 pA current injection. Action potential duration was calculated as the difference in the time from beginning of the action potential until the time that the membrane potential returned to within 10 mV of the resting membrane potential.

2.6. Measurement of cAMP production

Each tube containing 10 islets was incubated for 1 h at 37 °C in KRBH with 8.3 mM glucose containing 500 μmol/l 3-isobutyl-1-methylxanthine (IBMX) and 100 μmol/l 4-(3-butoxy-4-methoxybenzyl) imidazolidone (Ro 20-1724). IBMX and Ro 20-1724 are broad-range phosphodiesterase (PDE) inhibitors to avoid degradation of cAMP in the samples.

Suramin, SQ 22536 were applied during the experiment in the presence or absence of ADPβS. Forskolin (FSK), a cAMP agonist, was given as a positive control. Total cellular cAMP content in islets were determined by EIA kit (Institute of isotopes Co. Ltd, HU).

2.7. Statistical analysis

Data represent the mean ± SEM. Statistical analyses were performed using the Student's t-test or ANOVA tests as appropriate. P values below 0.05 were considered to have statistically significant difference.

3. Results

3.1. AC/cAMP/Epac signaling pathway mediates P2YR-regulated insulin secretion

Numerous P2YR agonists have been used to examine the P2YR-mediated effects on insulin secretion, and among them, ADPβS [adenosine-5′-O-(2-thiodiphosphate)] has been shown to potentiate glucose-stimulated insulin secretion more potently than others, suggesting that ADPβS is a useful tool for the investigation of the mechanism underlying P2YR-mediated insulin secretion [8,9]. Indeed, our experiment demonstrated that ADPβS significantly potentiated insulin secretion from isolated rat islets at high (8.3 or 16.7 mM) but not at low (2.8 mM) glucose conditions (Fig. 1A). To confirm that the effect of ADPβS on insulin secretion is mediated by P2YR, we treated rat islets with a P2YR antagonist, suramin. As predicted, the potentiated insulin secretion by ADPβS was blocked by suramin (Fig. 1B).

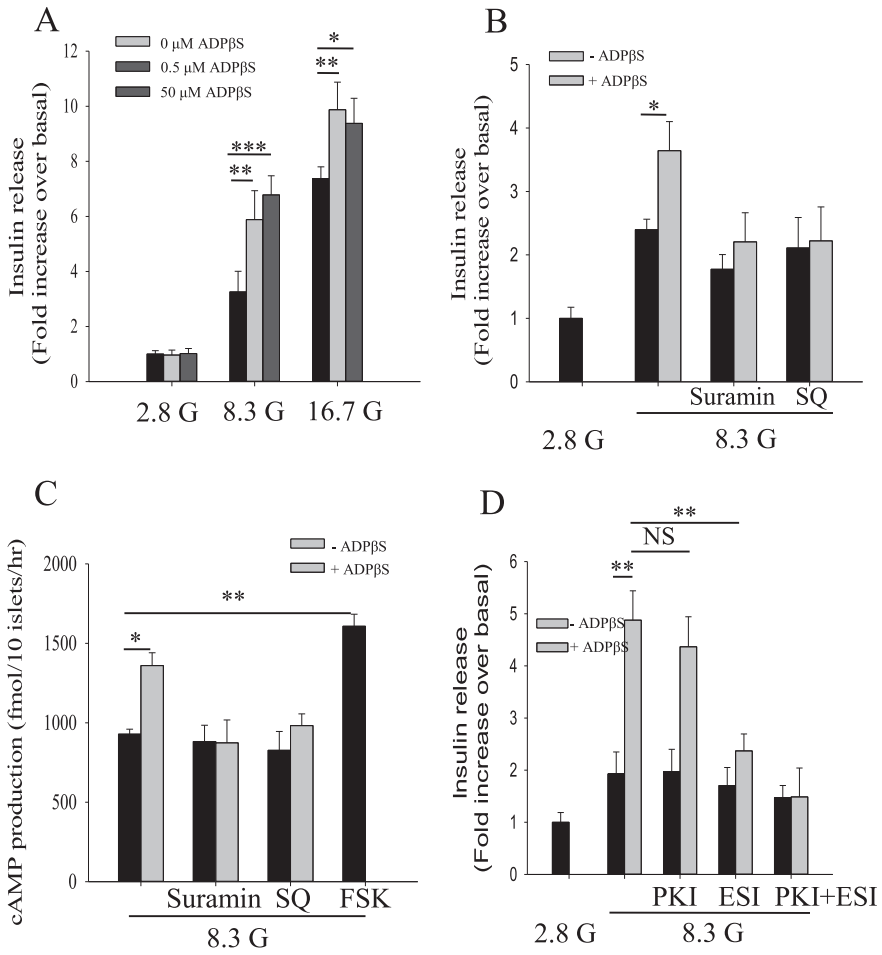

Fig. 1. Potentiation of insulin secretion by P2YR activation is mediated by AC/cAMP/Epac signaling pathway. (A) Effects of ADPβS on insulin secretion at different concentrations of glucose (2.8, 8.3 and 16.7 mM). (B) Effects of suramin (50 μM) and SQ 22536 (SQ, 10 μM) on insulin secretion at 8.3 mM glucose (8.3G) condition in the absence and presence of ADPβS (0.5 μM). (C) Effects of suramin (50 μM) and SQ 22536 (10 μM) on intracellular cAMP in the absence or presence of ADPβS (0.5 μM) at 8.3 mM glucose (8.3 G) condition. Forskolin (FSK, 10 μM) was applied as a positive control. (D) Effects of PKI (10 nM) and ESI-09 (ESI, 10 μM) on insulin secretion at 8.3 mM glucose condition. The experiments were repeated three times. $P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

In addition, SQ 22536, an adenylyl cyclase (AC) inhibitor also significantly blocked the effect of ADPβS on insulin secretion (Fig. 1B). AC is a crucial enzyme that catalyzes the synthesis of cAMP from ATP, we therefore measured cAMP content in rat islets to confirm our observations. As illustrated in Fig. 1C, ADPβS treatment elevated cAMP levels, and the effect could be eliminated by suramin and SQ 22536. These results are in support of previous reports, suggesting that the P2YR/AC/cAMP pathway plays an important role in regulating insulin secretion [10].

The effects of cAMP are mediated by two downstream effectors, protein kinase A (PKA) and Epac. We next wanted to identify the involvement of PKA and Epac in P2YR-mediated insulin secretion. As shown in Fig. 1D, Epac inhibitor ESI-09, but not PKA inhibitor PKI, significantly blocked the effect of ADPβS on insulin secretion, suggesting that Epac is a key downstream signaling component for P2YR-mediated insulin secretion. Therefore, it is of interest to identify how P2YR activation exerts effects through Epac to modulate insulin secretion.

3.2. Activation of P2YR prolongs action potential duration (APD)

Pancreatic β cells are electrically excitable cells; their excitability determines the β cell stimulus-secretion coupling [4]. Therefore we asked whether activation of P2YR influences β cell excitability. We investigated the effect of ADPβS on β cell electrical activity by monitoring electrically-induced action potentials. The current-clamp recordings showed that ADPβS remarkably lengthened APDs compared to control (Fig. 2). However, ADPβS combined with SQ 22536 did not influence APDs (Fig. 2). In addition, we have previously shown that SQ 22536 alone has no effect on APDs [7]. These data indicate that activation of P2YR plays a role to alter β cell excitability via the AC signaling pathway.

3.3. Kv channels are inhibited via the P2YR-mediated signaling pathway

Prolonged APD can result from either decreased repolarizing currents or increased depolarizing currents during action potential firing. In pancreatic β cells, the Kv channel is the major factor that is responsible for repolarizing currents. Of note, pharmacological inhibition and genetic ablation of K_V channel have been shown to potentiate insulin secretion in a glucose-dependent manner [5,6,11]. This led to the hypothesis that Kv channels are involved in P2YR-mediated signaling pathway.

We thus monitored K_V currents using the whole-cell voltage-clamp technique. The result demonstrated that K_V currents were significantly inhibited by ADPβS (Fig. 3A, B), suggesting that P2YR activation-induced prolongation of APD, at least partially, is due to

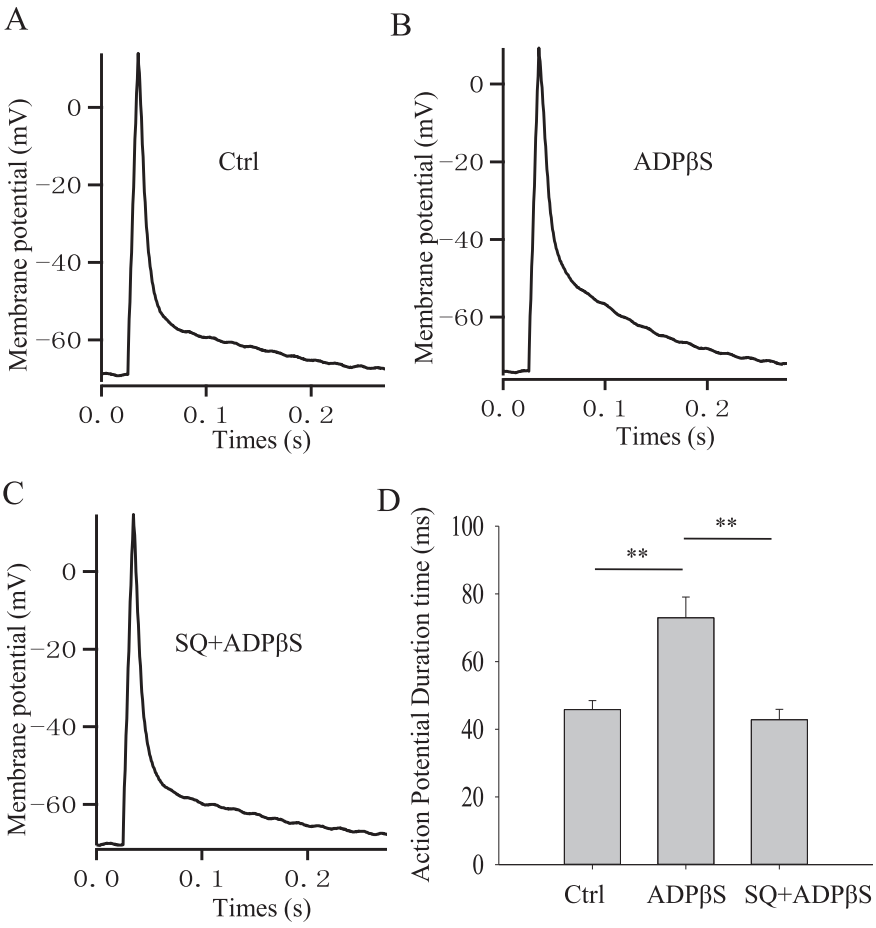

Fig. 2. Activation of P2YR prolongs action potential duration. Action potentials (APs) were elicited by applying 4 ms, 150 pA current injections. Representative action potential waveforms are shown for cells cultured with: (A) 11.1 mM glucose. (B) 11.1 mM glucose + 0.5 μM ADPβS. (C) 11.1 mM glucose + 10 μM SQ 22536 + 0.5 μM ADPβS. (D) Summary of mean APDs. The experiments were repeated six times. $^{**}P < 0.01$.

the inhibition of K_V channels. Furthermore, we found suramin or SQ 22536 reversed the effect of ADPβS on K_V channels (Fig. 3A–D). The data indicate that Kv channel is the downstream target of the P2YR/AC/cAMP signaling pathway in pancreatic β cells.

Based on our insulin secretion results described above, we then wondered if modulation of Epac influences the action of ADPβS on Kv channels. Consistent with our insulin secretion data, the results showed that ESI-09 abolished the effect induced by ADPβS, suggesting the Kv channel acts downstream of Epac (Fig. 3E, F).

3.4. Kv channels are involved in P2YR-mediated insulin secretion

Evidence demonstrates that inhibition of K_V channel potentiates insulin secretion in a glucose-dependent manner, i.e., K_V inhibition-potentiated insulin secretion only occurs at high glucose conditions [6,11,12]. This characterization is in concert with our results shown in Fig. 1A, that ADPβS significantly potentiated insulin secretion only at high (8.3 or 16.7 mM) but not at low (2.8 mM) glucose conditions, implying that the Kv channel is involved in P2YR-mediated insulin secretion. To further verify the involvement of the Kv channel in P2YR-mediated insulin secretion, we employed tetraethylammonium chloride (TEA), a potent K_V channel blocker, with or without ADPβS in the insulin secretion study. As expected, our data showed that TEA and ADPβS both independently potentiated insulin secretion at 8.3 mM glucose, but notably, ADPβS had no further effect on insulin secretion in the presence of TEA (Fig. 4A). These results suggest that the Kv channel is important in P2YR-mediated insulin secretion.

In pancreatic β cells, Ca^{2+} channels constitute the major factor that is responsible for depolarizing currents, which is important for insulin secretion and also for the maintaining of APD. We therefore asked if Ca^{2+} channels are involved in P2YR-mediated insulin secretion. As shown (Fig. 4B), the current–voltage relationship obtained in patch-clamp experiments demonstrated that activation of P2YR by ADPβS influence neither the current amplitude nor the voltage-dependent property of Ca^{2+} channels. The data indicate that Ca^{2+} channels may not be an important player in ADPβS-regulated insulin secretion.

3.5. Activation of P2YR increases $[Ca^{2+}]_i$ level

The elevation of $[Ca^{2+}]_i$ is essential for triggering β cell exocytosis. It has been demonstrated that blockade of K_V channels prolongs APD, and in turn, leading to augmentation of $[Ca^{2+}]_i$ [5,6,11]. We therefore determined the effect of ADPβS on $[Ca^{2+}]_i$ in pancreatic β-cells. As shown in Fig. 4C, addition of ADPβS caused elevation of $[Ca^{2+}]_i$, which could be eliminated by suramin (Fig. 4D) and SQ 22536 (Fig. 4E). To investigate the role of Kv channels in ADPβS-induced $[Ca^{2+}]_i$ elevation, we applied TEA before addition of ADPβS in a calcium imaging study. As shown in Fig. 4F, the Kv channel blocker TEA elevated $[Ca^{2+}]_i$, but the effect of ADPβS on $[Ca^{2+}]_i$ was erased in the presence of TEA. Considering that the Ca^{2+}

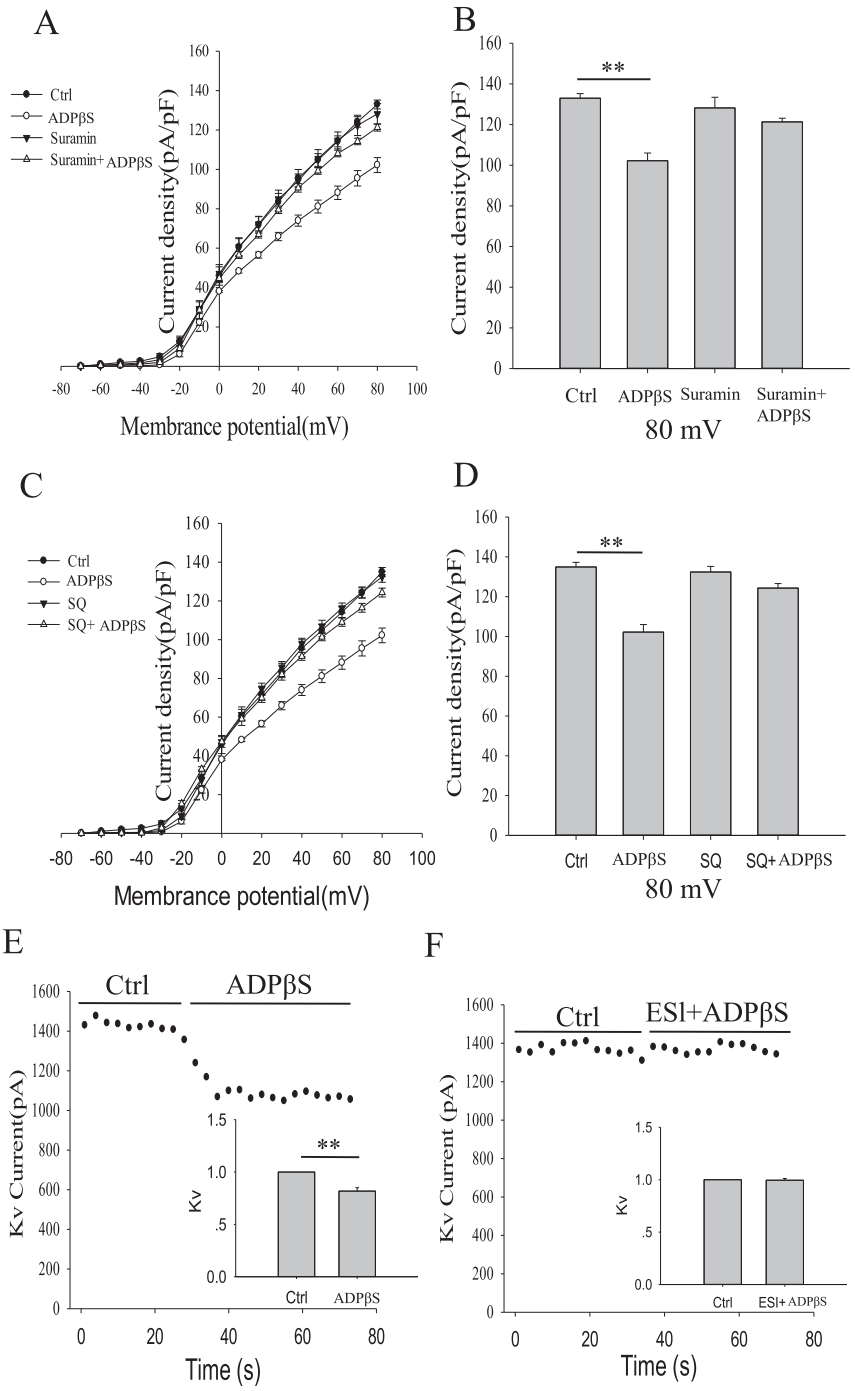

Fig. 3. Kv channels are involved in P2YR-mediated signaling pathway. (A, C) Current–voltage relationship curves of K_V channels obtained from rat beta cell under the different treatments as indicated. (B, D) Summary of the mean current density of K_V channels recorded at 80 mV depolarization. (E, F) Representative time–response curve of K_V currents in response to 400 ms voltage steps to +70 mV under the different treatments as indicated. The holding potential was −70 mV and voltage steps were applied every 3 s in perforated whole-cell configuration. The inset bar graph shows the normalized Kv currents to control. Control (Ctrl); ADPβS (0.5 μM); Suramin (50 μM); SQ 22536 (SQ, 10 μM); ESI-09 (ESI, 10 μM). The experiments were repeated 3 times. *P < 0.05, **P < 0.01.

channel was not altered by ADPβS, these findings indicate that the effect of ADPβS on $[Ca^{2+}]_i$ in β cells is, at least partly, mediated by the inhibition of K_V channels.

4. Discussion

P2YR activation potentiates insulin secretion in a glucose-dependent manner, this characterization makes P2YR a promising therapeutic target for diabetes. Exploring the mechanisms of P2YR-modulated insulin secretion is therefore beneficial in advancing our understanding of the biological regulation of insulin secretion.

In this report, we demonstrate that the AC/cAMP signaling pathway mediates the insulinotropic action of P2YR, which is in agreement with a previous report [10]. cAMP has been shown to be an important messenger in the coupling mechanisms of insulin secretion, and its two downstream effectors, PKA and Epac have

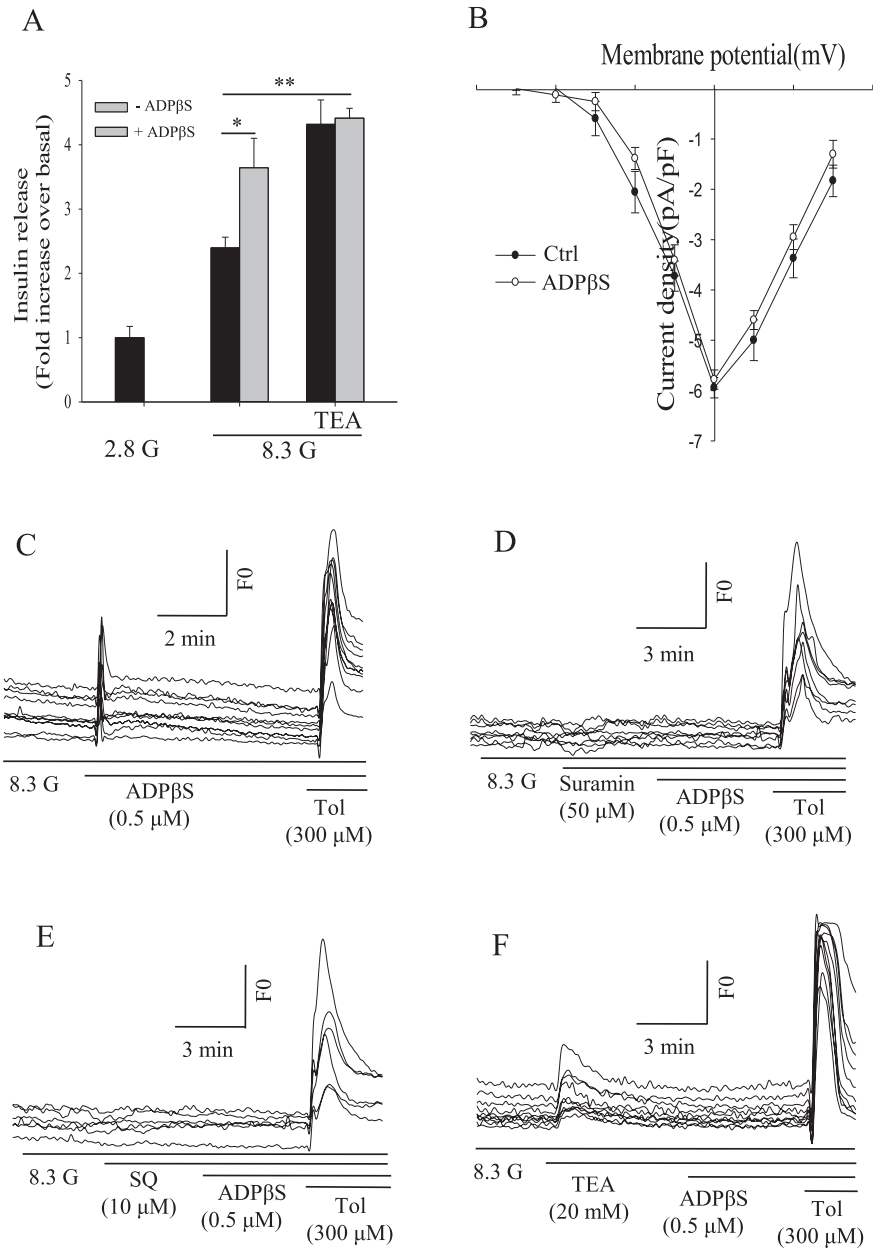

Fig. 4. K_V channels are involved in P2YR-mediated insulin secretion and $[Ca^{2+}]_i$ elevation. (A) Effects of ADPβS (0.5 μM) on insulin secretion in the absence or presence of TEA (20 mM) at 8.3 mM glucose (8.3 G) condition. The values were normalized to basal secretion at 2.8 mM glucose (2.8G). (B) Current–voltage relationship curves of Ca^{2+} channels under the treatments with or without ADPβS (0.5 μM). (C) $[Ca^{2+}]_i$ was measured with Fluo 4-AM using a laser scanning confocal microscope. Cells were treated with ADPβS at 8.3 mM glucose (8.3G) condition. (D) $[Ca^{2+}]_i$ was measured when cells were treated with suramin in the absence or presence of ADPβS at 8.3 mM glucose (8.3G) condition. (E) $[Ca^{2+}]_i$ was measured when cells were treated with SQ 22536 (SQ) in the absence or presence of ADPβS at 8.3 mM glucose (8.3G) condition. (F) $[Ca^{2+}]_i$ was measured when cells were treated with 20 mM TEA in the absence or presence of ADPβS at 8.3 mM glucose (8.3G) condition. Tolbutamide (Tol) was applied as a positive control. The experiments were repeated for four times. *$P < 0.05$, **$P < 0.01$.

been proposed to regulate insulin release in distinct ways [13]. Our results indicate that inhibition of Epac predominantly attenuated the P2YR-mediated insulin secretion, whereas inhibition of PKA shows no significant influence, although with inhibitory tendency, on P2YR-mediated insulin secretion. The data suggests that Epac is a key downstream signaling target for P2YR-mediated insulin secretion. This is supported, at least in part, by evidence from previous studies. First, Epac specific activator, 8-pCPT-AM can enhance glucose-dependent insulin secretion [14–17]. Second, Inhibition of Epac2 expression inhibits cAMP-induced increase in insulin secretion [18]. While PKA may have permissive effects on Epac action [14], the interest of the present study is how P2YR activation exerts effect through Epac to modulate insulin secretion.

We find that ADPβS potently inhibited the Kv channel, which is responsible for the prolonged APD due to the decreased repolarizing currents. Moreover, we show that this inhibitory effect on Kv current is mediated by P2YR/AC/Epac signaling pathway. The data are in line with previous findings performed in rat adult ventricle, where Epac activator has been found to prolong action potential duration by decreasing potassium current [19]. In neurons, inhibition of potassium current by stimulating P2YR has also been reported [20]. We thus believe that Kv channel may be the important

contributor that mediates P2YR-modulated insulin secretion, which is confirmed by our experiment in insulin secretion assays.

More importantly, inhibition of Kv channels has been reported to result in potentiation of insulin secretion in a glucose-dependent manner, because physiologically, the Kv channel is only open in response to membrane depolarization under high glucose condition [12]; inhibition of Kv channels causes prolongation of APD, leading to elevated $[Ca^{2+}]_i$ levels due to the removal of the Ca^{2+} entry limitation from K_V activation, and in turn potentiates insulin secretion [5,11]. This model is suitable to P2YR activation-induced inhibition of Kv channels. Thus, the current findings provide new insights into the glucose-dependent mechanisms underlying P2YR-modulated insulin secretion.

Gong et al. reported that ADPβS inhibited Ca^{2+} channel currents of rat β cells [21], which seems to be contradictory to our data. The reason for this difference is not clear, but it might be due to the concentration of ADPβS used. Gong et al. showed that addition of 15 μM ADPβS decreased Ca^{2+} current, while in the present study we show that 0.5 μM ADPβS has no effect on Ca^{2+} channels. Especially, we note that our experiments do show that 50 μM ADPβS has no further increased effect on insulin secretion compared to 0.5 μM ADPβS treatment at 16.7 mM glucose concentration, which might result from the Ca^{2+} channel inhibition. Further experiments are needed to verify this possibility.

Intravenous or oral administration of ADPβS was reported to improve glucose tolerance [1,22]. P2YR agonists also amplified insulin secretion in an in vitro pancreas preparation from Zucker diabetic rats [23]. Moreover, in human islet preparations, ADPβS was also successful in inducing glucose-dependent insulin secretion [2]. All these observations indicate that P2YR agonists or ADPβS-like analog might be good candidates for future therapeutic drug developments for T2D. The present study demonstrates that the cAMP/Epac/Kv channel pathway mediates P2YR-regulated insulin secretion, suggesting that targeting this pathway may be a therapeutic strategy for diabetes treatments.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors are grateful to Prof. Christian Holscher (Lancaster University) for reading the manuscript and providing invaluable comments.

This work was supported by grants to Y.Z from NSFC (81070662, 81273564), Natural Science Foundation of Shanxi Province (2012011039-8), Shanxi Scholarship Council of China (2012-046). This work was also supported by grants to Y.L from NSFC (81373464), Department of Health of Shanxi Province (201201062), Advanced Programs of Shanxi for the Returned Overseas Chinese Scholars, the clinical medicine special funds for scientific research projects from Chinese Medical Association (13040440429), the Ministry of Human Resources and Social Security (2013-277), the First Hospital of Shanxi Medical University (YC1422). NSFC (81270882 to J.Y) also supported this work.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.03.121.

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