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Vildagliptin, an Anti-diabetic Drug of the DPP-4 Inhibitor, Induces Vasodilation via Kv Channel and SERCA Pump Activation in Aortic Smooth Muscle

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Abstract

This study investigated vildagliptin-induced vasodilation and its related mechanisms using phenylephrine induced pre-contracted rabbit aortic rings. Vildagliptin induced vasodilation in a concentration-dependent manner. Pretreatment with the large-conductance Ca^{2+}-activated K^+ channel blocker paxilline, ATP-sensitive K^+ channel blocker glibenclamide, and inwardly rectifying K^+ channel blocker Ba^{2+} did not affect the vasodilatory effects of vildagliptin. However, application of the voltage-dependent K^+ (Kv) channel inhibitor 4-aminopyridine significantly reduced the vasodilatory effects of vildagliptin. In addition, application of either of two sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) inhibitors, thapsigargin or cyclopiazonic acid, effectively inhibited the vasodilatory effects of vildagliptin. These vasodilatory effects were not affected by pretreatment with adenylyl cyclase, protein kinase A (PKA), guanylyl cyclase, or protein kinase G (PKG) inhibitors, or by removal of the endothelium. From these results, we concluded that vildagliptin induced vasodilation via activation of Kv channels and the SERCA pump. However, other K^+ channels, PKA/PKG-related signaling cascades associated with vascular dilation, and the endothelium were not involved in vildagliptin-induced vasodilation.

Keywords Vildagliptin · Voltage-dependent K^+ channel · SERCA pump · Aortic smooth muscle

Introduction

Diabetes mellitus (DM) is a prevalent metabolic disease characterized by persistent hyperglycemia. According to International Diabetes Federation data, there were 415 million adult DM patients worldwide in 2015, and that number will increase to 642 million by 2040 [1]. Among these patients, most have type 2 DM. Therefore, numerous studies during recent decades have focused on developing type 2 anti-diabetic drugs. To date, several types of type 2 anti-diabetic drugs have been developed such as metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, sulfonylurea, meglitinide, α-glucosidase inhibitor, thiazolidinediones, sodium glucose co-transporter 2 inhibitor, and dipeptidyl peptidase-4 (DPP-4) inhibitors [2]. Among these drugs, DPP-4 is the most noteworthy treatment for type 2

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DM. As an oral anti-hyperglycemic, vildagliptin is a DPP-4 inhibitor that protects against bioactive incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), thereby potentiating insulin secretion [3]. Apart from its antiglycemic effects, vildagliptin improved vasodilation in patients with type 2 DM [4]. However, the detailed mechanisms of vildagliptin-induced vasodilation have not been studied.

Four major types of K^+ channels have been identified in vascular smooth muscle: inwardly rectifying K^+ (Kir), voltage-dependent K^+ (Kv), large-conductance Ca^{2+}-activated K^+ (BK_{Ca}), and ATP-sensitive (K_{ATP}) channels [5, 6]. Although each K^+ channel contributes to the regulation of vascular functions, Kv channels are important channels for maintaining resting membrane potential and resting tone [7, 8]. Furthermore, changes in Kv channel function are closely associated with many cardiovascular and metabolic diseases [9]. Therefore, improving Kv channel function considered a potential therapeutic target for the treatment of cardiovascular and metabolic diseases. In addition to Kv channels, intracellular Ca^{2+} also plays an important role in regulating vascular tone. In fact, increased intracellular Ca^{2+} strongly induces vasoconstriction and thereby various vascular diseases such as atherosclerosis and hypertension. Regulation of intracellular Ca^{2+} depends on activation of the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump. For this reason, several studies have suggested that changes in SERCA pump expression are associated with heart disease, hypertension, diabetes, and aging in animal models and humans [10].

Considering the therapeutic efficacy of vildagliptin in type 2 DM patients and the physiological relevance of vascular Kv channels and intracellular Ca^{2+}, it is essential to elucidate the association between vildagliptin-induced vasodilation and Kv channels and intracellular Ca^{2+}.

In this study, we demonstrated the vasodilatory effects of vildagliptin on the rabbit thoracic aorta. Vildagliptin-induced vasodilation occurred in a dose-dependent manner by activation of the Kv channel and SERCA pump. However, these effects were not associated with other K^+ channels, protein kinase A (PKA)- or protein kinase G (PKG)-related signaling pathways, or the endothelium.

Materials and Methods

Artery Preparation and Measurement

All experimental procedures were conducted in accordance with the guidelines of the Committee for Animal Experiments of Kangwon National University (Gangwon-do, South Korea). Male New Zealand White rabbits (1.9–2.2 kg) were anesthetized by intravenous administration of heparin (70 U/kg) and sodium pentobarbitone (50 mg/kg). The hearts were removed and placed in normal Tyrode's solution. The thoracic aorta was immediately isolated from the heart and separated from perivascular adipose and connective tissue under the stereomicroscope. The purified aorta was cut into transverse rings of ~ 10 mm in length. Aortic rings were mounted on the organ chamber with two stainless steel hooks. Once the rings were mounted, the organ chamber was filled with physiological salt solution (PSS), bubbled with 95% O_2 and 5% CO_2, and maintained at 37 °C. The aortic rings were sustained for at least 1 h at a resting tension of 1 g. In some experiments, the endothelium was disrupted by injection of air bubbles into the lumen. The absence of endothelium was confirmed by the inhibition of acetylcholine-induced vasodilation. High K^+-PSS (80 mM) was applied to investigate the viability of arteries.

Solutions and Chemicals

The normal Tyrode's solution contains the following (mM): KCl 5.5, NaCl 145, $CaCl_2$ 1.6, NaH_2PO_4 0.40, HEPES 5.8, $MgCl_2$ 0.6, and Glucose 20, adjusted to pH 7.4 with NaOH. PSS contains the following (mM): KCl 4.5, NaCl 115, $CaCl_2$ 1.6, $NaHCO_3$ 27, KH_2PO_4 1.5, $MgSO_4$ 1.3, and Glucose 20, adjusted to pH 7.4 with NaOH. Vildagliptin, Phenylephrine (Phe), 4-aminopyridine (4-AP), and $BaCl_2$ were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Acetylcholine, paxilline, glibenclamide, SQ 22536, ODQ, KT 5720, KT 5823, thapsigargin, and cyclopiazonic acid were purchased from Tocris Cookson (Ellisville, MO). All chemicals were dissolved in dimethyl sulfoxide (DMSO) or distilled water. The final concentration of DMSO had no significant effect on the vasodilatory effect of vildagliptin.

Data Analysis

Data were analyzed using Origin v.7.0 software (Microcal Software, Inc., Northampton, MA, USA). The results are presented as mean ± standard error of the mean; *n* is the number of arteries. Data were compared using Student's *t* test to evaluate statistical significance. *P* values less than 0.05 were considered statistically significant.

Results

Effects of Vildagliptin on Aortic Rings Precontracted by Phenylephrine

We investigated the vasodilatory effects of vildagliptin using aortic rings that had been precontracted with phenylephrine (Phe, 1 μM). As shown in Fig. 1a, application of vildagliptin induced vasodilation in a concentration-dependent manner.

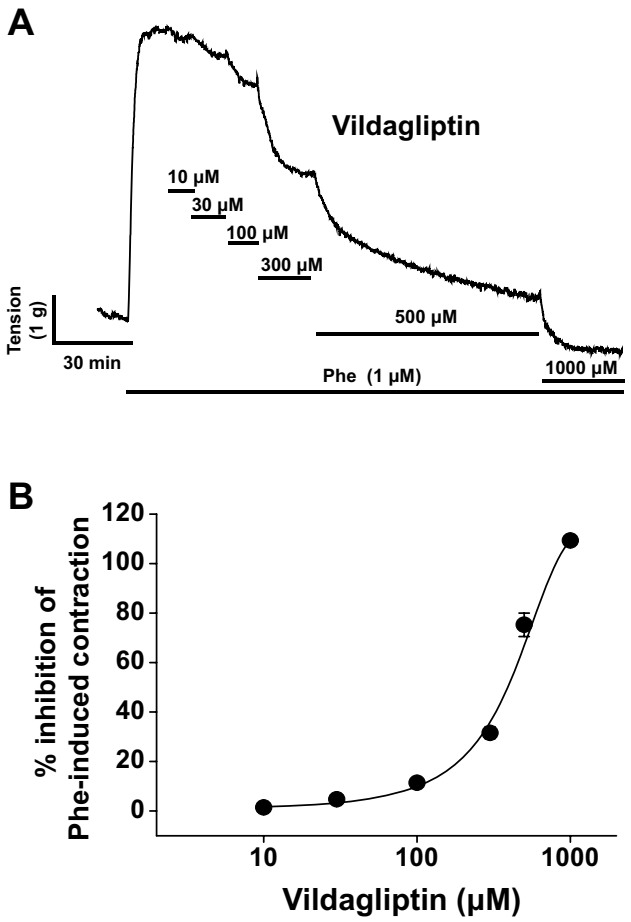

Fig. 1 The vasodilatory effects of vildagliptin on thoracic aortic rings from rabbits. **a** The representative traces were induced by diverse concentrations of vildagliptin (10, 30, 100, 300, 500, and 1000 μM) applied to Phe-induced precontracted aortic rings. **b** Concentration-dependent curve for vildagliptin-induced vasodilation. All $n = 10$, n represents the number of arteries isolated from different rabbits

For example, administration of 500 μM and 1000 μM vildagliptin induced vasodilation by 75.27% and 109.38%, respectively (Fig. 1b). Furthermore, 1,000 μM vildagliptin induced vasodilation to the baseline (before applying Phe), and no further vasodilation was observed with vildagliptin over 1000 μM.

Involvement of Vascular K^+ Channels in Vildagliptin-Induced Vasodilation

To test the association between vascular K^+ channels and vildagliptin-induced vasodilation, aortic sections were pretreated with four types of K^+ channel inhibitors before applying vildagliptin. As shown in Fig. 2a, pretreatment with the BK_{Ca} inhibitor paxilline (10 μM) did not alter the precontracted arterial tone. Furthermore, paxilline did not change the vasodilatory effects of vildagliptin (Fig. 2b). Similar to paxilline, application of the K_{ATP} channel inhibitor glibenclamide (10 μM) did not change the tone of arteries precontracted with Phe or the vasodilatory effects of vildagliptin (Fig. 2c, d). Application of the Kir channel inhibitor Ba^{2+} (50 μM) induced further vasoconstriction in aortic rings precontracted with Phe (Fig. 2e). However, pretreatment with Ba^{2+} did not change the vasodilatory response to vildagliptin (Fig. 2f). Similar to the results for Ba^{2+}, application of the Kv channel inhibitor 4-AP induced further vasoconstriction (Fig. 2g). However, pretreatment with 4-AP effectively reduced the vasodilatory effects of vildagliptin (Fig. 2h). These results suggest that the vasodilatory effects of vildagliptin on aortic rings were closely related to the activation of Kv channels but not BK_{Ca}, K_{ATP}, or Kir channels.

Intracellular Ca^{2+} Stores are Involved in Vildagliptin-Induced Vasodilation

To investigate the involvement of intracellular Ca^{2+} in vildagliptin-induced vasodilation, we used the SERCA pump inhibitors thapsigargin (1 μM) and cyclopiazonic acid (10 μM) to deplete the intracellular Ca^{2+} store. As shown in Fig. 3a, b, the pretreatment with thapsigargin reduced the vasodilatory response to vildagliptin. To confirm this result, we pretreated the aortic ring with another SERCA pump inhibitor, cyclopiazonic acid. Similar to the results for thapsigargin, pretreatment with cyclopiazonic acid (10 μM) effectively inhibited the vasodilatory response to vildagliptin (Fig. 3c, d). These results suggest that vildagliptin-induced vasodilation occurs by activating the SERCA pump.

Involvement of Adenylyl Cyclase and PKA in Vildagliptin-Induced Vasodilation

To determine whether the vasodilatory response to vildagliptin is associated with PKA-related signaling pathways, we applied an adenylyl cyclase inhibitor SQ22536 (50 μM) to inhibit the production of cAMP in the aortic rings precontracted with Phe. As shown in Fig. 4a, b, pretreatment with SQ22536 had no significant effects on the vasodilatory response to vildagliptin. To further evaluate the involvement of PKA-related signaling pathways in vildagliptin's effects, we pretreated the Phe-induced precontracted aortic rings with the PKA inhibitor KT5720 (1 μM), and found that this pretreatment did not affect the vasodilatory effects of vildagliptin (Fig. 4c, d). These results indicated that the vasodilatory effects of vildagliptin were not associated with the cAMP/PKA-related intracellular signaling pathway.

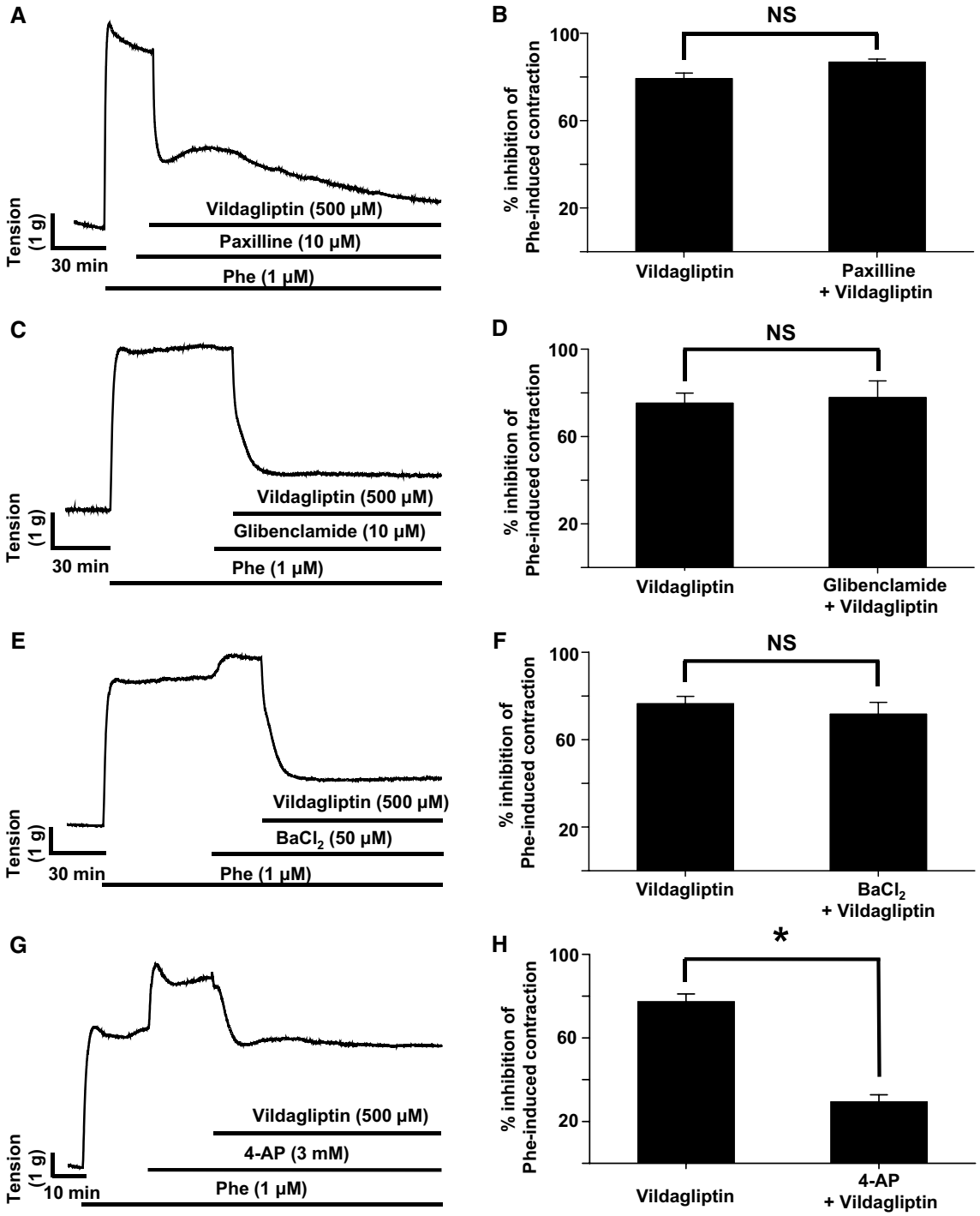

Fig. 2 Effects of vascular K^+ channel inhibitors on vildagliptin-induced vasodilation. **a** Effects of paxilline, a BK_{Ca} channel inhibitor, on vildagliptin-induced vasodilation. **b** Summary of the effects of paxilline on the vasodilatory response of vildagliptin. $n=4$. *NS* not significant. **c** Effects of glibenclamide, a K_{ATP} channel inhibitor, on vildagliptin-induced vasodilation. **d** Summary of the effects of glibenclamide on the vasodilatory effects of vildagliptin. $n=4$. *NS* not significant. **e** Effects of Ba^{2+}, a Kir channel inhibitor, on vildagliptin-induced vasodilation. **f** Summary of the effects of Ba^{2+} on the vasodilatory effects of vildagliptin. $n=4$. *NS* not significant. **g** Effects of 4-AP, a Kv channel inhibitor, on vildagliptin-induced vasodilation. **h** Summary of the effects of 4-AP on the vasodilatory effects of vildagliptin. $n=5$. $^*P<0.05$. All n represents the number of arteries isolated from different rabbits

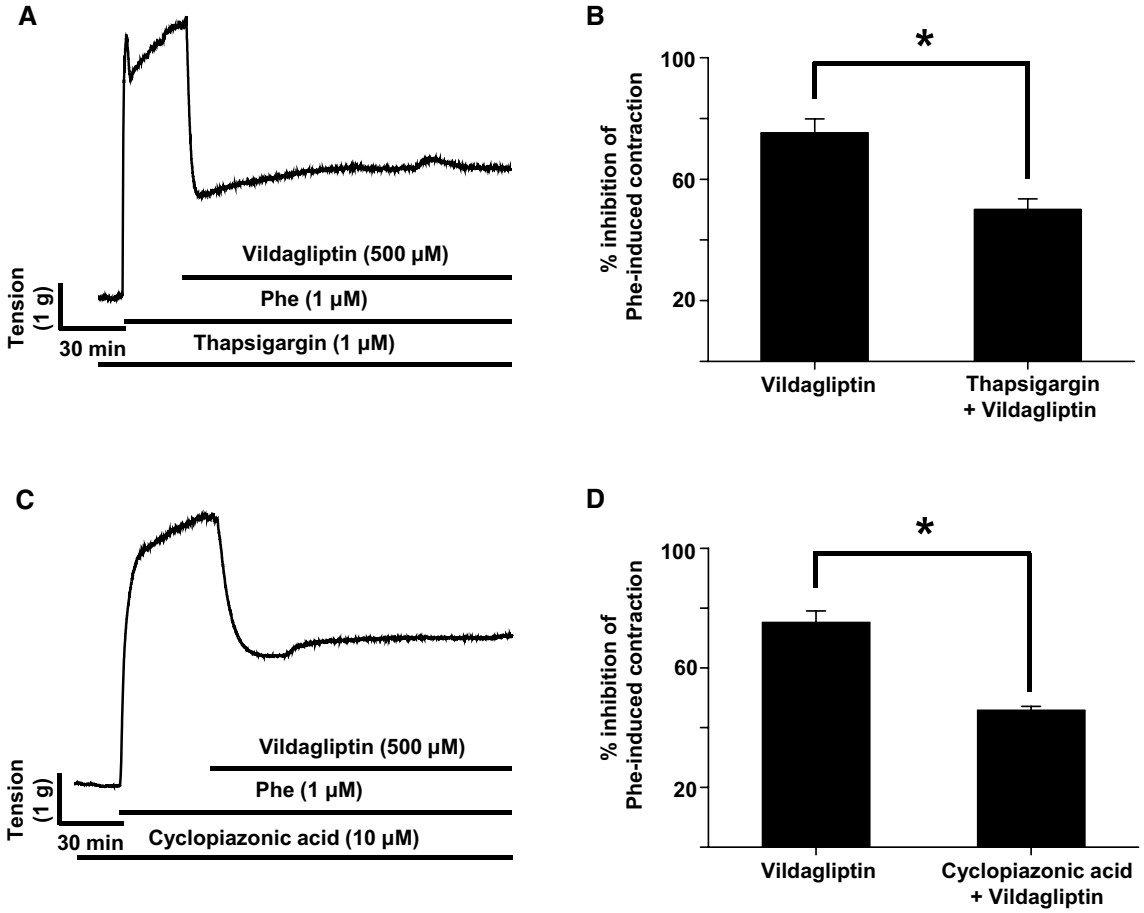

Fig. 3 Involvement of intracellular Ca^{2+} in vildagliptin-induced vasodilation. **a** Effects of thapsigargin, a specific SERCA pump inhibitor, on vildagliptin-induced vasodilation. **b** Summary of the effects of thapsigargin on the vasodilatory response to vildagliptin. $n=5$. $^*P<0.05$. **c** Effects of cyclopiazonic acid, another SERCA pump inhibitor, on vildagliptin-induced vasodilation. **d** Summary of the effects of cyclopiazonic acid on the vasodilatory effects of vildagliptin. $n=4$. $^*P<0.05$. All n represents the number of arteries isolated from different rabbits

Involvement of Guanylyl Cyclase and PKG in Vildagliptin-Induced Vasodilation

To identify the association between cGMP/PKG-related intracellular signaling pathway and vildagliptin-induced vasodilation, we applied the guanylyl cyclase inhibitor ODQ (1 μM) to the aortic rings precontracted with Phe and found that ODQ pretreatment had no noticeable effects on vildagliptin-induced vasodilation (Fig. 5a, b). Furthermore, application of the PKG inhibitor KT 5823 (1 μM) also fail to alter the vasodilatory effects of vildagliptin (Fig. 5c, d). From these results, we concluded that the vasodilatory response to vildagliptin was not associated with the cGMP/PKG-related intracellular signaling pathway.

Endothelium-Dependency on Vildagliptin-Induced Vasodilation

To determine whether the vasodilatory response of vildagliptin is caused by secretions from the endothelium, we measured the vasodilatory effects of vildagliptin using endothelium-denuded aortic rings. The successful removal of endothelium was confirmed by acetylcholine-induced further constriction in Phe-induced precontracted aortic rings. Figure 6a shows the vasodilatory effect of vildagliptin on endothelial-denuded aortic rings. The degree of vildagliptin-induced vasodilation did not differ between endothelium-intact and endothelium-denuded arteries (Fig. 6b). These results suggest that the vasodilatory effects of vildagliptin were independent of the endothelium.

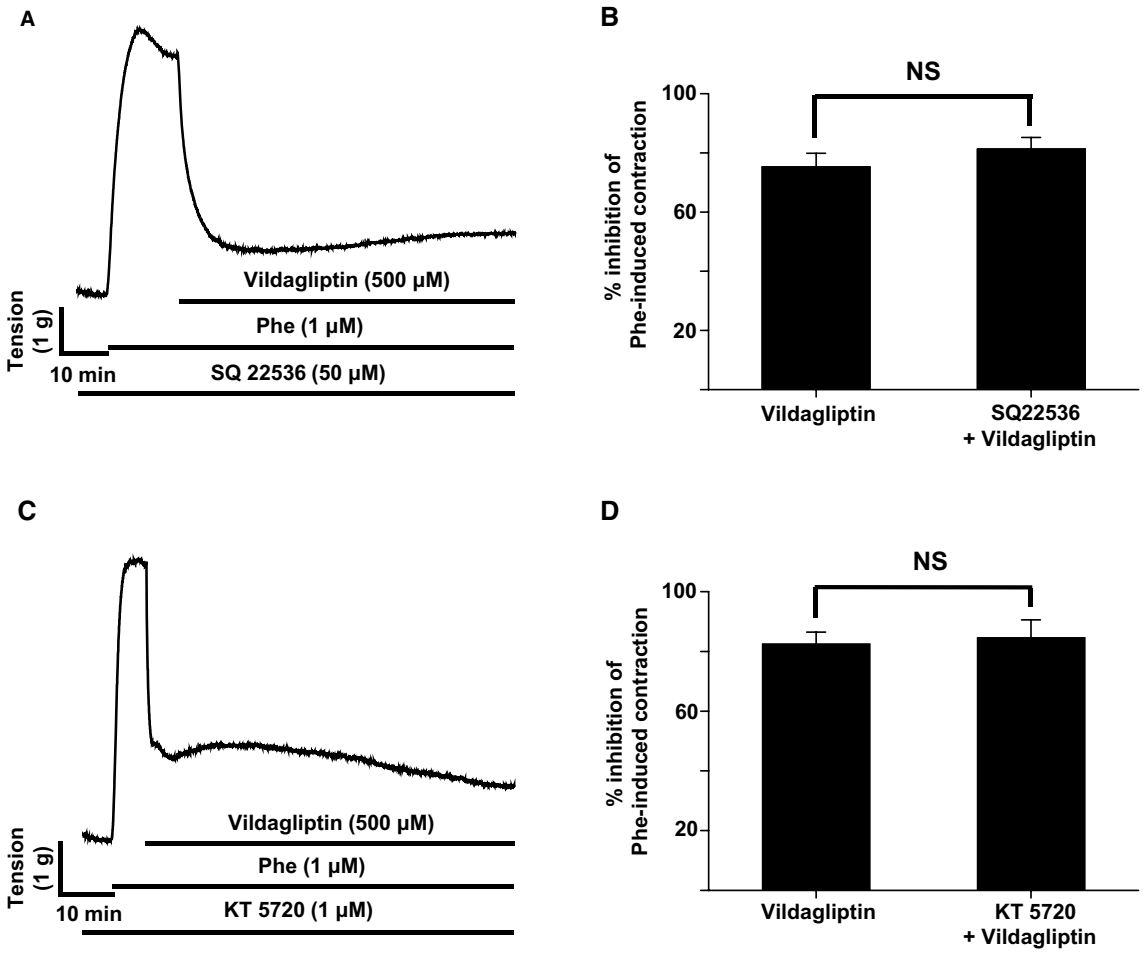

Fig. 4 Effects of an adenylyl cyclase or PKA inhibitor on vildagliptin-induced vasodilation. **a** Effects of SQ22536, an adenylyl cyclase inhibitor, on vildagliptin-induced vasodilation. **b** Summary of the effects of SQ22536 on the vasodilatory effects of vildagliptin. $n=4$. *NS* not significant. **c** Effects of KT5720, a PKA inhibitor, on vildagliptin-induced vasodilation. **d** Summary of the effects of KT5720 on the vasodilatory effects of vildagliptin. $n=5$. *NS* not significant. All n represents the number of arteries isolated from different rabbits

Involvement of the Kv1.5, Kv2.1, and Kv7 Subtypes in Vildagliptin-Induced Vasodilation

The vasodilatory effect of vildagliptin is found to be associated with Kv channel activation (Fig. 2). To further investigate the involvement of Kv subtypes on the vasodilatory effect of vildagliptin, we pretreated with the specific Kv1.5, Kv2.1, and Kv7 inhibitors DPO-1, guangxitoxin, and linopirdine, respectively, because these subtypes are known to be the major Kv subtypes in arterial smooth muscles [6, 11]. As shown in Fig. 7a, b, pretreatment of DPO-1 (1 μM) did not alter the vasodilatory effect of vildagliptin. In addition, application of guangxitoxin (100 nM) did not change the vasodilatory effect of vildagliptin (Fig. 7c, d). However, pretreatment with linopirdine (10 μM) effectively reduced the vasodilatory effect of vildagliptin (Fig. 7e, f). From these results, we can conclude that vildagliptin-induced vasodilation was due to the activation of the Kv channel, specifically the Kv7 subtype.

Discussion

This study investigated the vasodilatory mechanisms of vildagliptin using rabbit thoracic aortas. The vasodilatory response to vildagliptin was caused by activation of the Kv channel and SERCA pump. However, this effect was not associated with other K^+ channels, PKA/PKG-related signaling pathways, or the endothelium.

One of the most prevalent disorders in the world, DM, is caused by the inherited deficiency of insulin or acquired ineffectiveness of insulin. DM is roughly classified into type 1, type 2, and gestational DM. Among these, type 2 DM patients account for 90% of DM cases. Type 2 DM itself is

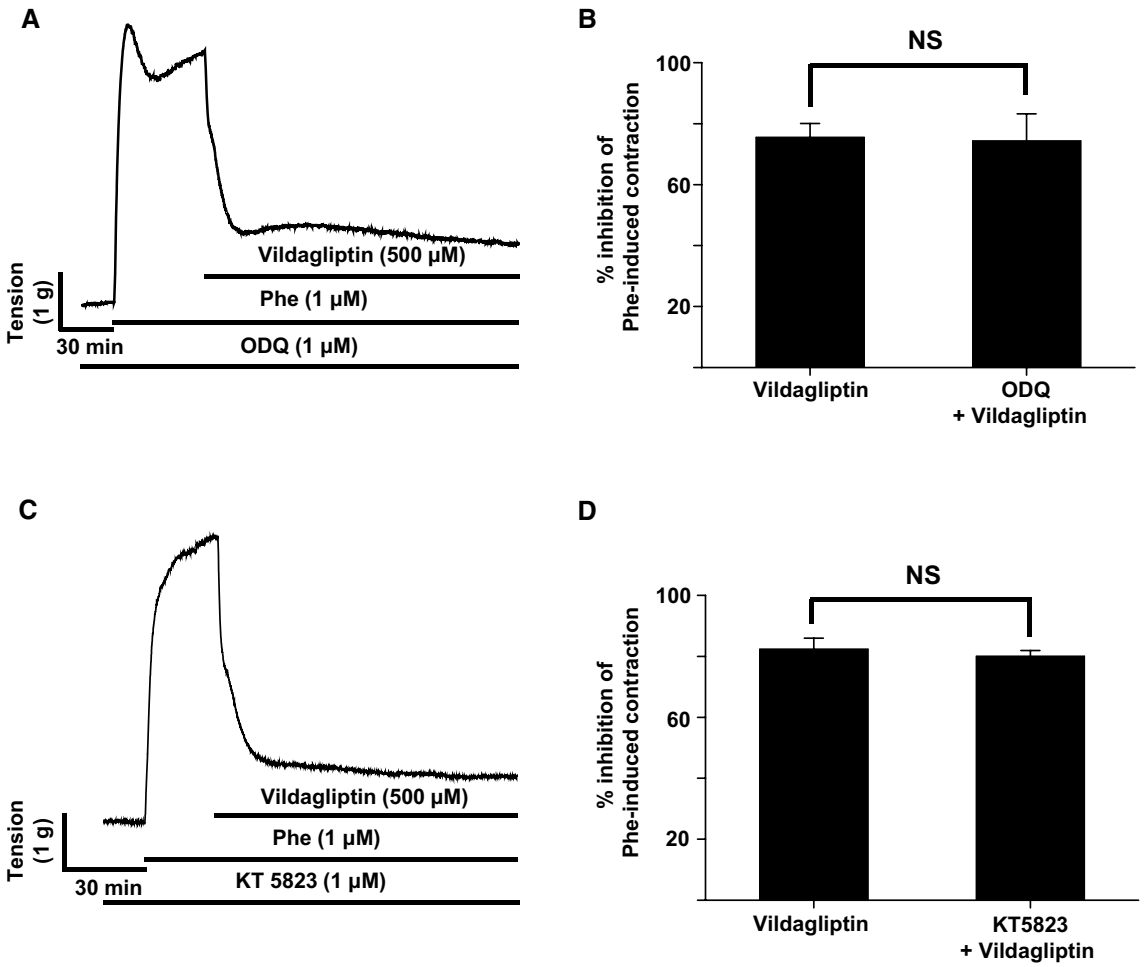

Fig. 5 Effects of a guanylyl cyclase or PKG inhibitor on vildagliptin-induced vasodilation. **a** Effects of ODQ, a guanylyl cyclase inhibitor, on vildagliptin-induced vasodilation. **b** Summary of the effects of ODQ on the vasodilatory effects of vildagliptin. $n=5$. *NS* not significant. **c** Effects of KT5823, a PKG inhibitor, on vildagliptin-induced vasodilation. **d** Summary of the effects of KT5823 on the vasodilatory effects of vildagliptin. $n=5$. *NS* not significant. All *n* represents the number of arteries isolated from different rabbits

a dangerous disease and can causes serious complications. Among the various complications reported, cardiovascular complications comprise the major cause of death in type 2 DM patients [12, 13]. To date, anti-diabetic drugs have been developed to control hyperglycemic conditions. However, most diabetic patients who are taking anti-diabetic drugs still fail to achieve proper glycemic control. Furthermore, several anti-diabetic drugs cause harmful side effects. For example, rosiglitazone and pioglitazone, a type of thiazolidinedione, can cause cardiovascular disease such as myocardial infarction and heart failure [14, 15]. Several sulfonylureas and the meglitinide class of drugs also induce hypoglycemia and weight gain [16, 17]. Compared to these drugs, vildagliptin has fewer side effects on the cardiovascular system and no side effects such as hypoglycemia and weight gain [18, 19]. In fact, vildagliptin was shown to decrease glycated hemoglobin without causing weight gain [20], and improved pancreatic (alpha and beta) islet cell responsiveness to glucose, thereby effectively controlling the blood glucose levels [21, 22]. Furthermore, a clinical study indicated that blood flow tended to be higher during orally administered vildagliptin (50 mg b.i.d.), accompanied by lower blood pressure [4]. However, the effects of vildagliptin on arterial dilation have not been investigated. Considering the clinical efficacy of vildagliptin for the treatment of type 2 DM and diabetic vascular complications, the vasodilatory effects of vildagliptin and its related signaling mechanisms should be clarified. In this study, we clearly demonstrated the vasodilatory mechanism of vildagliptin. Therefore, our findings could provide an explanation for vildagliptin-induced increase in blood flow and decrease in blood pressure.

To date, the physiological roles and electrophysiological properties of K^+ channels in vascular smooth muscle have been comprehensively identified. Four major types of K^+ (Kv, BK_{Ca}, K_{ATP}, and Kir) channels have been identified in vascular smooth muscle, and these channels are principal

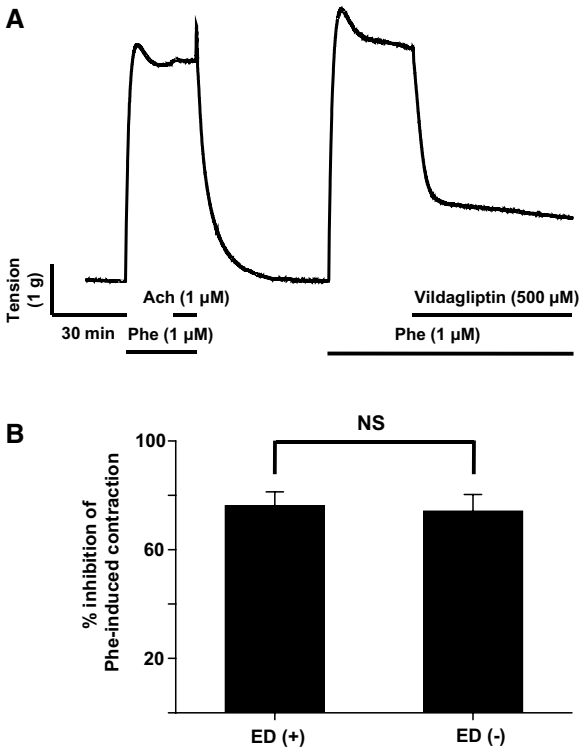

Fig. 6 Effects of vildagliptin on endothelium-denuded aortic rings. **a** Effects of vildagliptin on endothelial-denuded arteries. Acetylcholine induced further constriction and was used to confirm the successful removal of the endothelium. **b** Comparison of the vasodilatory effects of vildagliptin on endothelial-intact and denuded arteries. $n=4$. *NS* not significant. All *n* represents the number of arteries isolated from different rabbits

regulators of membrane potential and vascular tone [5, 6, 9]. In this study, we demonstrated that the vasodilatory effects of vildagliptin occurred through the activation of Kv channels, but not through other K^+ channels. Kv channels are highly expressed in most vascular smooth muscle cells, and are divided into several families (Kv1-12) according to genetic coding [23]. However, these subtypes have mainly been identified in human, mouse, and rat arteries, and the subtypes expressed in rabbit arteries remain unknown. Although the exact expression of Kv subtypes is obscure, previous studies have suggested that the Kv1.1, Kv1.2, Kv1.4, Kv1.5 Kv2.1, Kv7, and Kv9.3 subtypes are common in most arteries [6, 11, 24, 25]. Among these, the Kv1.5, Kv2.1, and Kv7 subtypes are the most prominent subtypes in the vascular smooth muscles [11, 26, 27], and inhibitors for these subtypes have been well developed. Therefore, we have tested the involvement of the Kv1.5, Kv2.1, and Kv7 subtypes on the vasodilatory response to vildagliptin by pretreatment with Kv1.5 subtype inhibitor DPO-1 (1 μM), Kv2.1 subtype inhibitor guangxitoxin (100 μM), and Kv7 subtype inhibitor linopirdine (10 μM). The inhibition by the Kv1.5 and Kv2.1 subtypes did not change the vasodilatory effect of vildagliptin. However, inhibition by the Kv7 subtype reduced the vasodilatory effect of vildagliptin (Fig. 7e, f). Based on these results, we suggest that the Kv7 subtype is the main target of vildagliptin among the diverse Kv subtypes. Although there may be other Kv subtypes involved in vildagliptin-induced vasodilation in other species, the expression of these Kv subtypes in rabbits is unknown. In addition, a lack of specific inhibitors of other Kv subtypes limited further experiments on the precise involvement of Kv subtypes in the vasodilatory effects of vildagliptin. Thus, additional studies on this issue are needed.

Ca^{2+} plays a crucial role in cellular functions such as excitation–contraction and excitation–transcription coupling in vascular smooth muscle cells. To maintain the homeostasis of intracellular Ca^{2+} concentration, the SERCA pump is essential. In fact, the SERCA pump is involved in cell growth and proliferation by controlling store replenishment of Ca^{2+}. In addition, increasing SERCA pump activity also can improve cardiac function and prevent cardiovascular disease [28]. In our study, pretreatment with SERCA pump inhibitors effectively reduced the vasodilatory effects of vildagliptin, which suggests that vildagliptin-induced vasodilation occurs by activation of the SERCA pump. Therefore, administration of vildagliptin may be effective for lowering blood sugar as well as lowering cardiovascular risks.

cAMP/PKA- or cGMP/PKG-related signaling pathways are among the most important mechanisms for relaxing blood vessels [29, 30]. In fact, several reports have indicated that the cAMP/PKA- and cGMP/PKG pathways are closely related with Kv channel and SERCA pump activity [9, 31]. Based on these findings, we evaluated the involvement of cAMP/PKA- or cGMP/PKG-related signaling pathways in vildagliptin-induced vasodilation using adenylyl cyclase, PKA, guanylyl cyclase, and PKG inhibitors, and found that the cAMP/PKA- and cGMP/PKG-related signaling pathways were not involved in vildagliptin-induced vasodilation. The vascular endothelium also serves important functions, regulating blood vessel tone by releasing vasodilators and endothelium-derived relaxing factors such as a nitric oxide (NO) [32]. In addition, endothelial and NO dysfunctions are associated with the onset of cardiovascular disease including hypertension, obesity, and diabetes [33]. Therefore, we examined the vasodilatory effects of vildagliptin on endothelium-denuded aortic rings to investigate the involvement of the endothelium. However, similar to the results for cAMP/PKA- or cGMP/PKG-related signaling pathways, the vasodilatory effects of vildagliptin were not changed by removal of the endothelium. Considering that the vasodilatory effects of vildagliptin were not associated with smooth muscle or endothelium-dependent signaling pathways, its effects likely occur by direct interaction with Kv channels and the SERCA pump. More precise interaction mechanisms should be addressed in future studies.

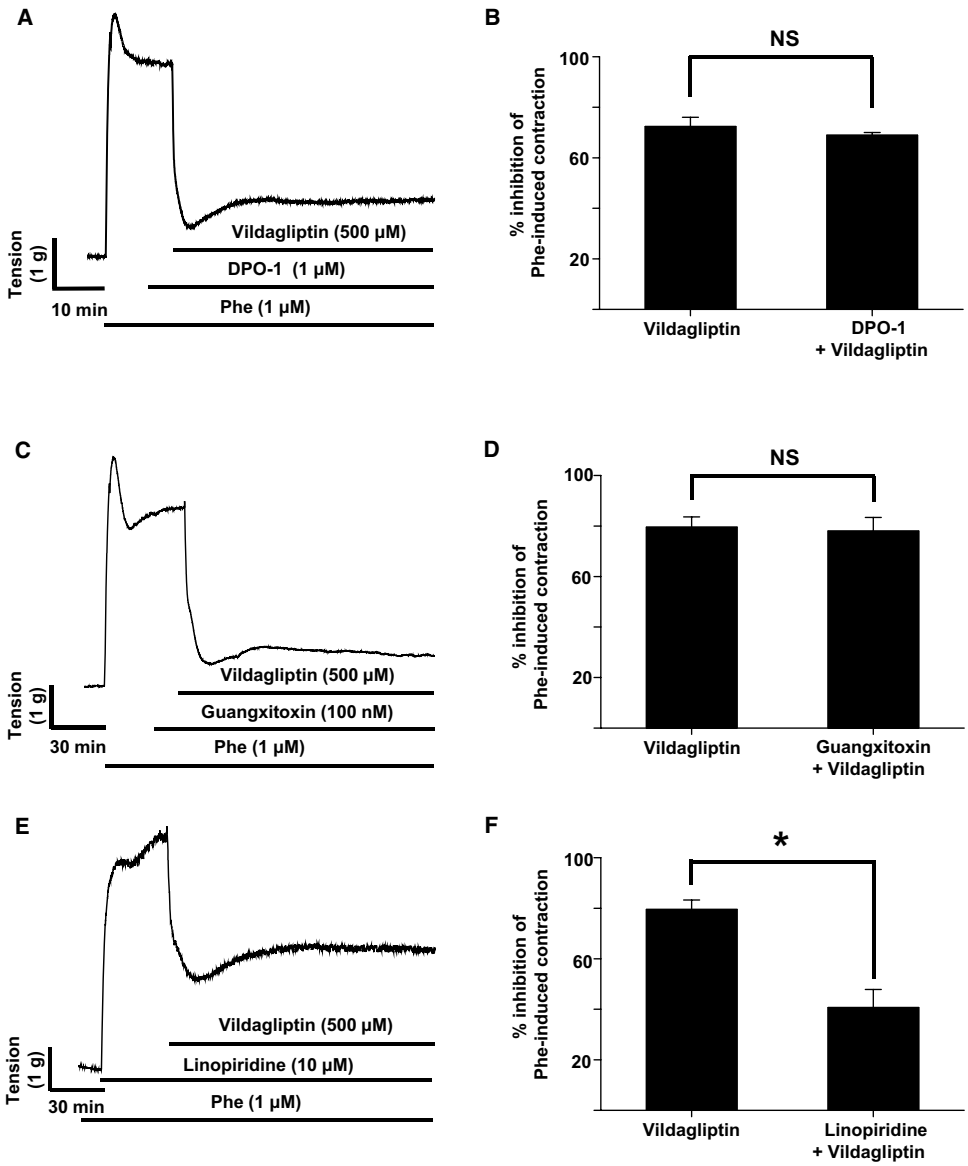

Fig. 7 Effects of the Kv1.5, Kv2.1, or Kv7 channel inhibitors on vildagliptin-induced vasodilation. **a** Effects of DPO-1, a Kv1.5 channel inhibitor, on vildagliptin-induced vasodilation. **b** Summary of the effects of DPO-1 on the vasodilatory effects of vildagliptin. $n = 5$. *NS* not significant. **c** Effects of guangxitoxin, a Kv2.1 channel inhibitor, on vildagliptin-induced vasodilation. **d** Summary of the effects of guangxitoxin on the vasodilatory effects of vildagliptin. $n = 4$. *NS* not significant. **e** Effects of linopirdine, a Kv7 channel inhibitor, on vildagliptin-induced vasodilation. **f** Summary of the effects of linopirdine on the vasodilatory effects of vildagliptin. $n = 4$. $^*P < 0.05$. All *n* represents the number of arteries isolated from different rabbits

The recommended dose of vildagliptin is 50 mg or 100 mg daily [34]. In monotherapy cases, doses of 100 mg once- or twice daily induce consistent and durable effects, including enhanced glycemic control [35]. Vildagliptin is rapidly absorbed, and achieves maximum plasma concentration (approximately 1.54–1.75 μM) within 1 to 2 h after administration; its elimination half-life is 2–3 h [34, 36, 37]. Our results showed that the vasodilatory effects of vildagliptin occurred at a concentration (> 30 μM) higher than the human maximum plasma concentration. However, lower concentrations (< 10 μM) of vildagliptin also induced vasodilation, although the degree of vasodilation was small. Furthermore, vildagliptin abuse or overmedication results in a higher maximum plasma concentration. Because the vascular smooth muscle has very large input resistance, minor vasodilation induced by vildagliptin may increase blood flow and decrease blood pressure. In addition, vildagliptin abuse or overdosing can further affect blood flow and pressure. Therefore, considering the vasodilatory effects of vildagliptin, vildagliptin is most effectively prescribed drug for patients with hypertension and diabetes. However, it should be prescribed with caution for patients with hypotension and diabetes.

In summary, this study demonstrated the vasodilatory mechanisms of vildagliptin in rabbit thoracic aortas. Our results showed that the vasodilatory effects of vildagliptin occurred through activation of the Kv channels and the SERCA pump. In addition, vildagliptin's effects were not associated with other K^+ channels, PKA/PKG signaling pathways, or the endothelium.

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Compliance with Ethical Standards

Conflict of interest The authors declare that there are no conflicts of interest

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