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SHORT COMMUNICATION

Vasorelaxant effects of forsythide isolated from the leaves of *Forsythia viridissima* on NE-induced aortal contraction

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Abstract

Forsythide (F1) isolated from the leaves of *Forsythia viridissima* (Oleaceae) showed vasorelaxant effects on norepinephrine (NE)-induced contraction of rat aorta with or without endothelium. This compound did not affect contraction induced by high concentration potassium (60 mM K^+) and phorbol 12,13-diacetate, but inhibited NE-induced contraction in the presence of nicardipine. These results demonstrated the inhibitory effects of F1 on NE-induced vasocontraction presumably due to decrease of calcium influx from extracellular area, which was induced by NE.
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Keywords: *Forsythia viridissima*; Forsythide; Iridoid; Vasorelaxant activity; ROC

Introduction

Forsythia viridissima and *F. suspensa* are listed in Japanese Pharmacopoeia as the original plants of Forsythiae fructus. Earlier studies revealed that *F. viridissima* constituents demonstrate a broad spectrum of medicinal properties including anti-inflammatory, diuretic and anti-hypertensive activities (Nishibe, 2002). Moreover, constituents such as lignans, phenylethanoids, and flavonoids were previously isolated from these species (Tokar and Klimek, 2005). In our earlier studies, two vasorelaxing constituents, forsythiaside from *F. suspensa* and acetoside (F2, Fig. 1) from *F. viridissima,* were isolated and elucidated their vasorelaxing activities via receptor-operated Ca^{2+}-channels (ROCs) inhibitor (Wong et al., 2001; Iizuka and Nagai, 2005; Iizuka et al., 2005). In the present study, we isolated another active constituent, forsythide (F1, Fig. 1), an iridoid derivative from the leaves of *F. viridissima*, and demonstrated vasorelaxing activities of forsythide on isolated rat aorta, compared with F2 as a positive control.

Materials and methods

Plant material

F. viridissima was identified by Dr. Nishibe at Health Science University of Hokkaido and dried leaves of *F. viridissima* were generously donated by Dr. Deyama in Yomeishu Seizo Co., Ltd. (Japan).

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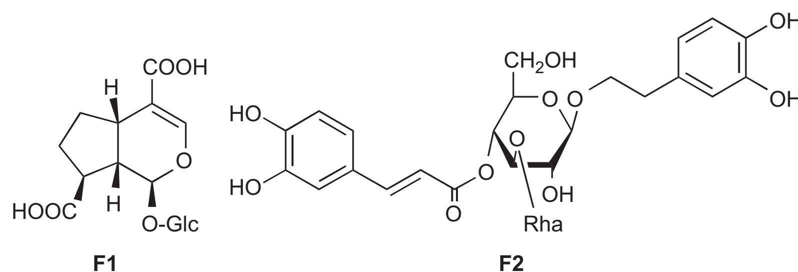

Fig. 1. Structures of compound F1 and F2.

Chemicals

NE, nicardipine, ethyleneglycol-bis-(β-aminoethyl ether)-tetraacetic acid (EGTA), phorbol 12,13-diacetate(PDA), and acetylcholine chloride (Ach) were all purchased from Sigma Chemical (St. Louis, MO, USA).

Equipment

Melting points were determined on a Yanagimoto microscopic melting point apparatus and are uncorrected (Yanagimoto, Japan). ^{1}H (500 MHz) -and ^{13}C (125 MHz) -NMR spectra were measured with a JEOL JNM-LA 500 spectrometer (JEOL, Japan), while chemical shifts are given on the δ scale (ppm) with tetramethylsilane (TMS) as an internal standard.

Extraction and isolation

The extraction, isolation and confirmation of F1 and F2 were described in previous studies (Iizuka and Nagai, 2005; Iizuka et al., 2005). The purity of F1 and F2 were more than 98% based on HPLC analysis. The preparatory HPLC system as follows: pump, LC-6AD (Shimadzu, Japan); detector, S-310A model-2 (Soma, Japan) at 254 nm; column, YMC ODS-AQ 250 $\times$ 20 mm i.d. (YMC Co. Ltd., Japan); mobile phase, 1% formic acid:MeCN (88:18–88:12–94:6). NMR-spectra and m.p. of F1 were identical with those in the literature (Damtoft et al., 1994; Wu et al., 2004).

Isolation of rat aortic strips

These animal experimental studies were conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University, and under the supervision of the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Male Wistar rats (Tokyo Laboratory Animals Science) weighing 240–340 g were housed in a room maintained at 23 ± 1 °C with a 12 h light/dark cycle (lights on 8:00 am to 8:00 pm). Food and water were available *ad libitum*. After 7–10 days of habituation, rats were killed by exsanguination from the carotid arteries under anesthesia. A section of the thoracic aorta between the aortic arch and the diaphragm was removed and placed in oxygenated, modified Krebs-Henseleit buffer (KHB: NaCl 118.0 mM, KCl 4.7 mM, $NaHCO_3$ 25.0 mM, $CaCl_2$ 1.8 mM, NaH_2PO_4 1.2 mM, $MgSO_4$ 1.2 mM, and glucose 11.0 mM). The aorta was cleaned and cut in ring preparations 3 mm in length or cut into helical strips 3 mm in width and 20 mm in length. To detach the endothelium, endothelial cells on each strip were removed by gentle rubbing of the endothelial surface with a disposable cotton applicator.

The tissue was placed in a well-oxygenated (95% O_2, 5% CO_2) bath of KHB 10 ml at 37 °C with the ringed aorta connected to a tissue holder and to a force–displacement transducer (Nihon Kohden, Japan, TB-611T). The tissue was equilibrated for 60 min under a resting tension of 1.0 g. During this time, the KHB solution in the tissue bath was replaced every 20 min at 37 °C.

Experimental protocol

Experiments were performed according to method as described in our previous studies (Nagai et al., 1996; Iizuka and Nagai, 2005; Iizuka et al., 2005, 2006). After equilibration, each aortic ring was contracted by treatment with NE 3×10^{-7} M. The presence of functional endothelial cells was confirmed by demonstrating relaxation with response to Ach 10^{-5} M, and aortic rings in which 80% relaxation occurred was considered as tissue with endothelium. The endothelial cells removed by rubbing were confirmed by observing the loss of Ach-induced relaxation. When the NE-induced contractions reached a plateau, each sample was added cumulatively. When NE-induced contractions in the presence of F1 were examined, thoracic aortic strips were exposed to F1 (10^{-4} M) for 1 h and then NE was added to the afore-mentioned bath. For examination of the contraction in depolarized muscle, normal KHS in the tissue bath was replaced to KHS containing high concentration

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