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A potential calcium antagonist and its antihypertensive effects

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ABSTRACT

Imperatorin (Imp) as a hypotensive active ingredient, its hypotensive effect was evaluated in the SHRs, its calcium antagonism and affinity to L-type calcium channel was also confirmed. The results showed that the blood pressure was decreased in the SHRs treated with Imp, the aortic ring was relaxed with Imp, L-type calcium channel currents and intracellular calcium free ion rise was nearly disappeared when adding Imp. In addition, Imp displayed a chromatographic peak similar to nitrendipine and verapamil by the cell membrane chromatography, same results from protein–drug docking approaches. Hence, Imp target the L-type calcium channel, and may be used as a novel antihypertensive drug.

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1. Introduction

The prevalence of hypertension [1,2] has increased dramatically in China and in other countries during the past decades [3–5]. Calcium antagonist [6,7] is a major class of antihypertensive drugs, and main role in the L-type calcium channel. There are only three subclasses of calcium blockers, including the dihydropyridines, the benzothiazepines and the phenylalkylamines. Calcium channels activity is a key determinant of vascular smooth muscle (VSM) contractile state [8–10], and L-type calcium channels are the classic target of calcium antagonists [11].

In recent years, the potential value of herbal medicines has been rediscovered. In the past, about 25% of the drugs prescribed worldwide come from plants, 121 such active compounds being in current use [12]. Although few plant-derived molecules are "prescribed" in the Western sense of the term outside of anti-tumor agents, and the number of "approved drugs" from plants over the last 30 years is below 10, and with one exception, all in cancer treatment. Of the 252 drugs considered as basic and essential by the World Health Organisation, 11% is exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors. Hence, in our lab based on the Prof. He established affinity membrane chromatography [13], active ingredient have been discovered from natural products.

Imperatorin (9-(3-methylbut-2-enyloxy)-7H-furo [3, 2-g] chromen-7-one, Imp; Fig. 1A), a dietary furanocoumarin, is widespread and found not only in the medicinal plant such as *Cnidium monnieri cuss* and *Angelica dahurica*[14–17], but also in popular culinary herbs such as *parsnip*, *parsley*, and *fennel*. Despite its occurrence in edible plants, Imp shows potent pharmacological activity and has been studied for its anti-inflammatory, antitumoral, anticonvulsant activities and potent vasodilatory effects [18–21]. Although a growing understanding of the mechanisms by which Imp acts on the vasculature [19], the precise molecular mechanisms through

Abbreviations: 2-APB, 2-aminoethoxydiphenyl borate; $[Ca^{2+}]_i$, the concentration of the intracellular free calcium; [Imp], the concentration of Imp; BP, blood pressure; CMC, cell membrane chromatography; DBP, diastolic blood pressure; DMEM, Dulbecco's modified Eagle's medium; DMSO, dimethyl sulfoxide; EGTA, ethylene glycol tetra-acetic acid; I_{CaL}, L-type calcium channel currents; Imp, Imperatorin; Nit, nitrendipine; PE, phenylephrine; SBP, systolic blood pressure; SHRs, spontaneously hypertensive rats; Ver, verapamil; VSM, vascular smooth muscle; WKY, Wistar–Kyoto rats.

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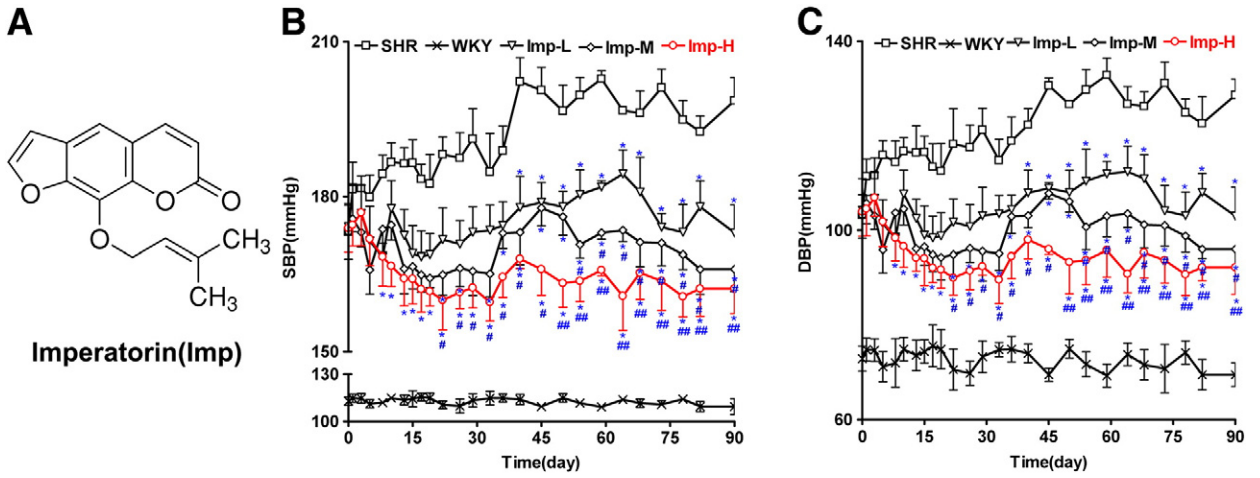

Fig. 1. Antihypertensive effect of Imp in spontaneously hypertensive rats (SHRs). (A) Chemical structure of imperatorin (Imp). (B) Effect of Imp on the systolic blood pressure (SBP), and (C) on the diastolic blood pressure (DBP). The three doses of Imp were expressed as Imp-H (▽), Imp-M (◇) and Imp-L (○), SHRs group and WKY group as placebo groups were expressed as SHR (□) and WKY (×). (n = 10 to 12). ★$P<0.01$ compared with SHRs, and $^{\#}P<0.05$, $^{\#\#}P<0.01$ compared with Imp-L.

which Imp relaxes VSM are not fully understood, and the hypotensive effect of Imp is also needed for proof.

2. Materials and methods

2.1. Instruments and materials

The chromatographic system consisted of a SPECTRA SERIE P200 chromatographic pump, a SPECTRA 100 detector (Thermo Separation Products, USA), a 7125 hand sampling valve (Rheodyne, USA), and an ANASTAR chromatographic work station (AOTAI Technology Co. limited, Tianjin). In this study, glass-bottom dishes (diameter: 36 mm, Shengyou Biotechnology Company, Limited, Hangzhou, China), column chromatography silica gel (Qingdao Ocean Chemical Plant, China) and macroporous ball silica (3–5 μm, 100 Å; Institute of Chemistry of the Chinese Academy of Sciences, China) were also used. The composition of the Krebs solution was (mM): NaCl 119, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1; $NaHCO_3$ 25; KH_2PO_4 1.2; and -glucose 11. The composition of the Krebs–Henseleit solution was (mM): NaCl 118.0, $NaHCO_3$ 25.0, KH_2PO_4 1.18, $MgSO_4$ 1.18, $CaCl_2$ 2.5, glucose 10.0 (pH 7.4). The composition of the phosphate-buffered saline (PBS) was (mM): NaCl 136.8, KCl 2.7, Na_2HPO_4 10, KH_2PO_4 1.8 at pH 7.2 titrated with NaOH. Ca^{2+}-free Krebs solution was prepared by omitting $CaCl_2$ and adding 0.5 mM ethylene glycol tetra-acetic acid (EGTA) instead. Fluo 3-AM was purchased from Biotium (Hayward, CA, USA). Bay K 8644 was purchased from Tocris (Tocris cookson Ltd., Bristol, UK). Nitrendipine (Nit; Shaanxi Xiyue Pharmacy Co., Ltd, China), Verapamil (Ver; Jiangsu Hengrui medicine Co.,Ltd, China) and Gefitinib (Nanjing Ange Pharmaceutical, China) were bulk drugs.

All other reagents and solvents were of analytical reagent grade and were used without further purification unless otherwise noted. All aqueous solutions were prepared using newly double-distilled water. Imp (patent number: ZL 2006 1 0042997.2, Langchong He, China; purity >98%) dissolved in 0.5% sodium carboxymethyl cellulose was for animals, in PBS (<0.1% dimethyl sulfoxide (DMSO)) or in Dulbecco's modified Eagle's medium (DMEM, <0.1% DMSO) as other additives were used on the rest of studies.

2.2. Animals

The SHRs and the Wistar–Kyoto (WKY) rats purchased from the Chengdu Da Shuo Biological Technology Company (Chengdu, China) have been used throughout this study. They were housed and maintained at 24 °C ± 2 °C in the humidity-controlled room (50% ± 10%) with a 12-h light–dark cycle. The animal had free access to standard pellet diet and water. All animal care and these experimental studies were conducted with the approval of the institutional guidelines of the Animal Experimental Center of Xi'an Jiaotong University (Xi'an, China) and conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication No. 85–23, revised 1996). The study was also approved by the Ethics Committee of Xi'an Jiaotong University.

2.3. Treatment protocol

There were four groups of the SHRs (male and 14-week-old): the placebo group (SHR, 0.5% sodium carboxymethyl cellulose per day, ig) and the three dosages Imp-treated groups (Imp-H, Imp-M and Imp-L; 25, 12.5 and 6.25 mg/kg Imp per day; ig). The placebo-treated WKY rats were used as the normotensive controls. Blood pressure (BP) was assessed along the 13 week treatment period with a tail-cuff apparatus (Coda-VPR, Kent Scientific, Torrington, CT, USA), after which they were euthanized.

2.4. In-vitro pharmacology

2.4.1. Artery ring experiments

The SHRs, male and 170–220 g, was euthanized. Thoracic aorta was gently excised and immediately stored in ice-cold Krebs–Henseleit solution previously gassed with 95% O_2/5% CO_2. Fat and connective tissue were removed, and the aorta

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