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Direct vascular actions of quercetin in aorta from renal hypertensive rats

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Abstract

Background: Chronic treatment with the dietary flavonoid quercetin is known to lower blood pressure and restore endothelial dysfunction in animal models of hypertension. This study investigated the direct effects of quercetin on vascular response in chronic 2-kidney, 1-clip (2K1C) renal hypertensive rats. The effects of antioxidant vitamin ascorbic acid on the vasoreactivity were also examined.

Methods: 2K1C renal hypertension was induced by clipping the left renal artery; age-matched rats that received sham treatment served as controls. Thoracic aortae were mounted in tissue baths for the measurement of isometric tension.

Results: Relaxant responses to acetylcholine were significantly attenuated in 2K1C rats in comparison with sham rats. Quercetin or ascorbic acid augmented acetylcholine-induced relaxation in 2K1C rats, whereas no significant differences were noted in sham rats. The relaxation response to sodium nitroprusside was comparable between 2K1C and sham rats, and sodium nitroprusside–induced relaxation was not altered by quercetin or ascorbic acid in either group. The contractile response to phenylephrine was significantly enhanced in 2K1C rats compared with sham rats. Phenylephrine-induced contraction was inhibited by pretreatment with quercetin or ascorbic acid in 2K1C rats, whereas neither chemical affected responses in sham rats. N^{w}-nitro-L-arginine methyl ester markedly augmented the contractile response to phenylephrine in sham rats, whereas no significant differences were observed in 2K1C rats. Quercetin or ascorbic acid did not affect phenylephrine-induced contraction in the presence of N^{w}-nitro-L-arginine methyl ester in either 2K1C or sham rats.

Conclusion: Acute exposure to quercetin appears to improve endothelium-dependent relaxation and inhibit the contractile response, similar to the effect of ascorbic acid in 2K1C hypertension. These results partially explain the vascular beneficial effects of quercetin in renal hypertension.

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Introduction

Hypertension, a typical risk factor of cardiovascular disease, involves endothelial dysfunction in large conduit and small resistance arteries [1]. Indeed, impaired endothelium-dependent vasodilation was observed in a number of experimental models of hypertension, including 2-kidney, 1-clip (2K1C) renal hypertension [2–4]. The biological activity of nitric oxide (NO), an effective endothelium-derived relaxing factor, is primarily associated with endothelial NO synthase activity or its interaction with the superoxide anion, which is produced in the vascular wall by free radical–generating enzymes [5]. Endothelium-derived NO may be scavenged by the superoxide anion, causing reduced bioavailability of NO and diminishing vasorelaxation [6]. It is now well established that endothelial dysfunction in hypertension is partially linked to the exaggerated production of superoxide anions [7,8] and that oxidative stress is responsible for impaired endothelial modulation in 2K1C hypertension [9,10]. Therefore, antioxidants may exert beneficial effects on the vascular complications associated with hypertension.

Quercetin is a commonly found flavonol-type flavonoid that is widely distributed in dietary vegetables, fruits, and wine [11]. Previous studies have demonstrated that the flavonoid quercetin has various physiological effects including antioxidant and antihypertensive effects as well as those associated with improvements in vascular reactivity [12,13]. The vascular beneficial effects induced by quercetin are mainly due to its antioxidant properties, which might interact with the endothelium-derived NO system [14]. Accumulated evidence demonstrates that flavonoids increase the biological activity of NO by interacting with superoxide anions [15], and chronic oral treatment with quercetin in experimental hypertension was shown to protect against impairments in vascular endothelial function [16]. Apart from the chronic effects of flavonoids associated with endothelial dysfunction in hypertension, acute exposure to quercetin *in vitro* restores endothelium-dependent relaxation and inhibits the contractile responses to the agonist in genetically hypertensive rats [11,17]. For this point of view, although it has been demonstrated that chronic treatment with quercetin exerts antihypertensive and antioxidant effects and improves endothelial function in renovascular hypertension [18], the acute effects of quercetin on vascular function in renal hypertension remain unclear.

The present study aimed to examine the direct effects of quercetin on vascular reactivity in chronic 2K1C hypertensive rats. The effects of quercetin on endothelium-dependent or endothelium-independent relaxation in response to acetylcholine or sodium nitroprusside (SNP) and the contractile responses to the α_1-adrenergic agonist phenylephrine were investigated in isolated aortae from 2K1C hypertensive and sham-clipped control rats. The effects of the antioxidant vitamin ascorbic acid (vitamin C) on vascular reactivity were also examined.

Methods

Induction of 2K1C renal hypertension

Male Sprague-Dawley rats (Samtaco Inc., Osan, Korea), weighing 160–180 g, were anesthetized with intraperitoneal injection of sodium thiopental (40 mg/kg). Under antiseptic conditions, the left posterior side of the animal was shaved and sterilized with 70% ethanol. An incision was made on the left flank to provide access to the left renal artery, which was separated from the renal vein and cleaned of connective tissue. A silver clip with an internal diameter of 0.2 mm was applied on the exposed renal artery. The clip was then turned so that the slit opening faces the abdomen, resulting in partial occlusion of renal perfusion. The contralateral kidney was not disturbed. The muscles and skin were sutured immediately, and the rats were allowed to recover from anesthesia. Control rats received a sham treatment: they underwent the same surgical procedure as 2K1C rats, except for clip placement. All rats were maintained on standard chow with free access to drinking water. They were killed for examination at 10 weeks after clipping because endothelial dysfunction is associated with the duration of hypertension [19]. Hypertensive rats were selected by measuring systolic blood pressure in the conscious state using the tail cuff method; they were considered hypertensive when the systolic pressure was over 160 mmHg.

Tissue preparation

At the time of experimentation, the descending thoracic aorta between the aortic arch and diaphragm was excised through a ventral incision and placed in cold, standard physiological salt solution of the following composition (in mM): NaCl 118.3, KCl 4.7, $NaHCO_3$ 25.0, $MgCl_2$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, and glucose 11.1. Vessels were cleaned of adherent fat and connective tissues and sectioned into cylindrical rings (2–3 mm in width) under a dissecting microscope. Care was taken not to stretch the artery or dislodge the vascular endothelium.

The aortic rings were mounted between two triangle-shaped stainless steel holders in the vessel lumen in organ chambers containing 15 mL of physiological salt solution maintained at 37 ± 0.05°C, aerated with a mixture of 95% oxygen and 5% carbon dioxide to maintain a pH of 7.4 ± 0.01 throughout the experiment. One of the holders was fixed at the bottom of the chambers and the other was connected to a force displacement transducer (Grass FTO3, Quincy, Mass, USA) to measure isometric tension development. Before initiating specific experimental protocols, aortic rings were stretched to the point of their optimal length–tension relationship at 2 g, determined in similar preliminary experiments using repeated exposure to 60mM KCl solution (obtained by equimolar replacement of NaCl by KCl in the physiological solution), and allowed to equilibrate for a period of at least 90 minutes. During this period of stabilization, the bath solution was replaced every 15 minutes. After an equilibration period, aortic rings were stimulated with 60mM KCl to test their functional viability. All experimental procedures were performed in the presence of indomethacin (10^{-5}M).

Protocols

Endothelium-dependent and endothelium-independent relaxation in response to acetylcholine and SNP were examined using aortic rings from 2K1C and sham-operated rats under submaximally precontracted with phenylephrine (2×10^{-7}M in sham and 3×10^{-8}M in 2K1C), based on doses obtained in preliminary experiments. The responses of the aortic rings to the cumulative addition of acetylcholine (from 10^{-9} to 10^{-5}M) and SNP (from 10^{-10} to $10^{-6.5}$M) were examined in parallel

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