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Protective effect of zingerone on increased vascular contractility in diabetic rat aorta

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ABSTRACT

The aim of the present study was to investigate the effect and possible mechanism of action of zingerone, the main constituent of ginger, on vascular reactivity in isolated aorta from diabetic rats. The results show that incubation of aortae with zingerone alleviates the exaggerated vasoconstriction of diabetic aortae to phenylephrine, as well as the impaired relaxatory response to acetylcholine in a concentration-dependent manner. Furthermore, Zingerone directly relax phenylephrine-precontracted aortae. The vasorelaxatory response is significantly attenuated by the nitric oxide synthase inhibitor Nω-nitro-L-arginine methyl ester hydrochloride and the guanylate cyclase inhibitor methylene blue but no effect of either the potassium channels blocker tetraethylammonium chloride, or the cyclooxygenase inhibitor indomethacin was observed. Zingerone had no effect on advanced glycation end product formation as well. In conclusion, zingerone ameliorates enhanced vascular contraction in diabetic aortae which may be mediated by its vasodilator effect through NO– and guanylate cyclase stimulation.

1. Introduction

It is well established that vascular disease is a complicating feature in patients with diabetes mellitus and responsible for its morbidity and mortality (Christrieb, 1973; Schalkwijk and Stehouwer, 2005). These vascular complications may be partially attributed to impairment of vasomotor function of smooth muscles (Nugent et al., 1996). In this respect, the reactivity of vascular smooth muscles to contractile and vasorelaxant agents in diabetic rats has been previously studied (Kamata et al., 1989; Stanley et al., 2013). Many studies have investigated the mechanism of the enhanced contractile response of diabetic blood vessels but the mechanism of enhancement is still unknown. However, an impaired endothelial activity (MacLeod, 1985), increased response to Ca^{2+} (Buluc et al., 2006), and increased production of vasoconstrictor prostanoids prostaglandin F_2 alpha, prostaglandin H_2 or thromboxane A_2 due to increased superoxide anion (Kanie et al., 2000) might be responsible for the increased contractile responses in diabetic rat vessels. In addition, the generation of reactive oxygen species (ROS) within the vascular wall scavenges nitric oxide (NO), decreasing its ability to stimulate soluble guanylate cyclase (sGC) and hence produce cGMP (Guerci et al., 2001).

Herbal medicines have recently attracted the interest of scientific communities as alternative therapy. The rhizome of *Zingiber officinale* (ginger) is consumed worldwide as a spice and flavoring agent. Zingerone is a phenolic alkanone which is present in a significant amount of about 9% in ginger (Zhang et al., 2012). Previous studies have showed that zingerone has anti-inflammatory and antioxidant effects (Kim et al., 2010). In addition, zingerone was found to inhibit contractile movements of isolated colonic segments (Iwami et al., 2011). Although these useful effects have been demonstrated, the molecular mechanism of zingerone on relaxation of smooth muscle was not fully studied and poorly understood. Therefore, the aim of this study is to examine the effect and potential mechanism of action of zingerone on aortae from diabetic rats.

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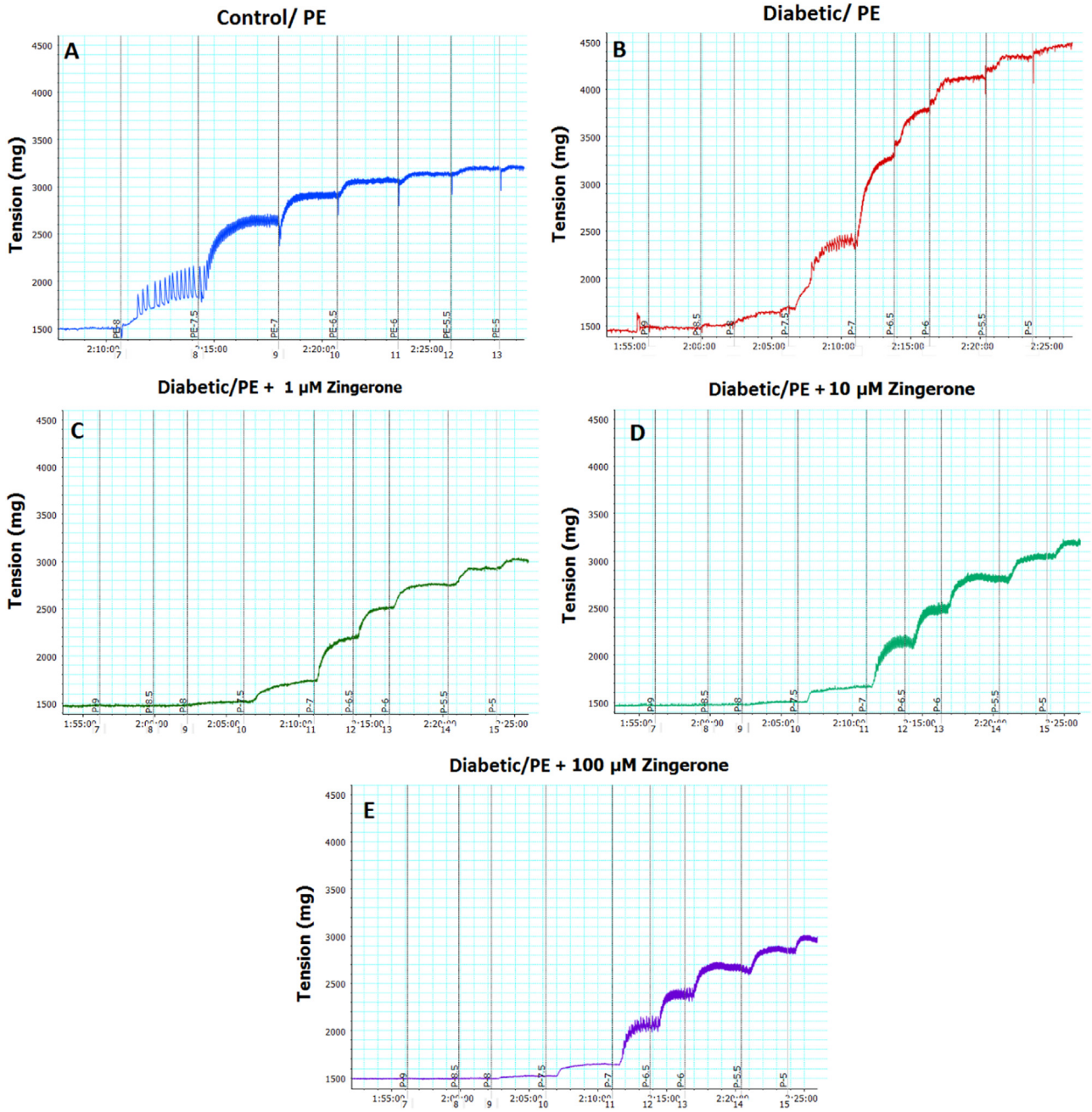

Fig. 1. Representative racing showing the vasoconstrictor response to phenylephrine (PE) in control rats (A), the exaggerated vasoconstrictor response in diabetic rats (B) and the ameliorative effect of different concentrations of zingerone (C, D and E).

2. Materials and methods

2.1. Drugs and chemicals

Zingerone, Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME), methylene blue (MB), tetraethylammonium chloride (TEA), indomethacin (INDO), aminoguanidine (AG), ribose, bovine serum albumin (BSA), acetylcholine and phenylephrine (PE) were purchased from Sigma-Aldrich Chemical company (Munich, Germany). 4-amino-5-methylamino-2′,7′-difluorofluorescein (DAF-FM) diacetate was purchased from Molecular Probes (New York, USA). All chemicals were dissolved in ultrapure deionized water except for zingerone and DAF-FM diacetate, which was dissolved in dimethylsulphoxide (DMSO). The final DMSO concentration did not exceed 0.1%, which has no effect on vascular reactivity according to our preliminary studies.

2.2. Animals and grouping

Male Wistar rats (King Abdulaziz University, Saudi Arabia) weighing 120–140 g, 6 weeks age, were housed in clear polypropylene cages (3–4 rats per cage) and kept under constant environmental conditions with equal light–dark cycle. Rats had free access to commercially available rodent pellet diet and purified water. All the experimental procedures were performed in accordance with Saudi Arabia Research Bioethics and Regulations, which are consistent with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. The experimental protocol was approved by the Unit of Biomedical Ethics, Faculty of Medicine, King Abdulaziz University. Animals were randomly divided into two experimental groups; control (C) and Diabetic (D) groups (6-8 rats in each group). Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ, 50 mg/kg). Glucose levels in tail blood were determined using a glucose meter (ACCU-CHEK, Roche, Mannheim, Germany) with noble metal electrode strips. Diabetes was confirmed by a stable hyperglycemia (blood glucose levels of 250–350 mg/dl) after 2 weeks of STZ injection. Rats were left for an additional 8 weeks to develop vascular complications based upon results of recent work from our laboratories (El-Bassossy et al., 2012).

2.3. Vascular reactivity

Vascular reactivity was assessed using the isolated artery technique previously described in previous work of our laboratories (El-Bassossy et al., 2013, 2014;