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Original article

Modulatory effect of vanillic acid on antioxidant status in high fat diet-induced changes in diabetic hypertensive rats

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ABSTRACT

The worldwide incidence of diabetes has increased dramatically along with widespread lifestyle and dietary changes. Diets high in fat are strongly associated with the development of obesity and can induce insulin resistance in humans and animals. It is clear that obesity constitutes a risk factor for contributing to the development of type 2 diabetes. In the present study, we investigated the therapeutic potential action of vanillic acid on diabetes associated complications using a rat model. Rats were made diabetic hypertensive by high fat diet (HFD) for 20 weeks and were treated with vanillic acid (50 mg/kg bw) for last 8 weeks. The effects of vanillic acid on glucose, plasma insulin, systolic and diastolic blood pressure, thiobarbituric acid reactive substances (TBARS), hydroperoxides as a lipid peroxidation marker, and the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), vitamin C and vitamin E as an antioxidant marker, AST and ALT as a liver function marker, urea, uric acid and creatinine as a kidney function marker were investigated. Histopathology of liver and kidney was also investigated as part of the pathology of diabetes. Treatment of diabetic rats with oral administration of vanillic acid at a dose of 50 mg kg/body weight for 8 weeks resulted in a significant decrease in fasting plasma glucose, insulin and blood pressure levels in comparison with diabetic control group. The antioxidant activities were significantly increased and the levels of lipid peroxidation markers were significantly decreased in diabetic hypertensive rats treated with vanillic acid. These results suggest that vanillic acid offer a modulatory effect on control of diabetic hypertension by reduction of blood glucose, insulin and blood pressure, combating oxidative stress by activation of tissue antioxidants.

1. Introduction

Diabetes mellitus and hypertension are interconnected diseases that strongly predispose an individual to atherosclerotic cardiovascular disease. Hypertension is about twice as frequent in persons with diabetes as in those without [1,2]. Lifestyle and genetic factors are important factors contributing to both hypertension and diabetes mellitus. The prevalence of coexisting hypertension and diabetes appears to be increasing in industrialized nations because populations are aging and both hypertension and NIDDM incidence increases with age [2]. Data obtained from death certificates show that hypertensive disease has been implicated in 4.4% of deaths coded to diabetes, and diabetes was involved in 10% of deaths coded to hypertensive disease. Indeed, an estimated 35% to 75% of diabetic cardiovascular and renal complications can be attributed to hypertension [1]. For all these reasons, hypertension and diabetes should be recognized and treated early and aggressively. Essential hypertension accounts for the majority of hypertension in individuals with diabetes, particularly those with NIDDM [type II diabetes], who constitute more than 90% of people with a dual diagnosis of diabetes and hypertension [1,2].

Oxidative stress constitutes a unifying mechanism of injury in many types of vascular diseases. It has been reported that hyperglycemia increases oxidative stress through overproduction of reactive oxygen radicals [ROSs] [3–5]. Free radicals are very reactive chemical species, can cause oxidative injury to the living beings by attacking the macromolecules like lipids, carbohydrates, proteins and nucleic acids. There is much evidence concerning the contribution of ROS molecules to organ injury in systems, such as heart, liver, and central nervous system [6–8], as well as that oxidative damage is increased in diabetes [9]. On the other hand, it

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is accepted that ROSs, generated as a result of hyperglycemia, play a role in many secondary complications of diabetes [10]. Among the cellular effects of oxidative stress is lipid peroxidation, DNA oxidation, protein oxidation, dysregulation of nitric oxide synthesis [11].

Cells possess enzymatic and nonenzymatic antioxidant systems to neutralize ROS [12]. Superoxide dismutase enzyme [SOD] converts superoxide anions to hydrogen peroxide [H_2O_2], and H_2O_2 can be rapidly removed by glutathione peroxidase [GPx] or by catalase, the major H_2O_2 detoxifying enzyme. Glutathione [GSH] is another major antioxidant that provides reducing equivalents for glutathione peroxidase [GPx]-catalyzed reduction of H_2O_2 and lipid hydroperoxides.

Under normal physiological conditions, there is a critical balance in the generation of oxygen free radicals and antioxidant defense systems used by organisms to deactivate and protect themselves against free radical toxicity [13]. Impairment in the oxidant/antioxidant equilibrium creates a condition known as oxidative stress. Oxidative stress is known to be a component of molecular and cellular tissue damage mechanisms in a wide spectrum of human diseases [14,15].

Nowadays the agents used for diabetes hypertension usually come with considerable side effects, such as hypoglycemia, drug-resistance, dropsy, weight gain [16]. In contrast, hundreds of traditional folk medicines have demonstrated potential for the treatment of diabetes with less tolerability and side effects. Thus, there is an increasing need to search for more natural antidiabetic agents from the traditional medicine. Many studies have reported that micronutriments such as polyphenols, vitamins, and minerals prevent or at least attenuate damage caused by oxidative stress. Polyphenols are the most abundant antioxidants in the diet [17]. and it has been demonstrated that they clearly improve the status of different oxidative stress biomarkers [18].

Vanillic acid (Fig. 1) is a phenolic derivative from edible plants and fruits known to possess antimicrobial, antifilarial [19] and antibacterial [20] effects. The chemical name of vanillic acid is 4-hydroxy-3-methoxy benzoic acid. It is an oxidized form of vanillin (4-hydroxy-3-methoxybenzaldehyde) [21], exhibits several bioactive properties such as antioxidant [22], and antimicrobial activities against yeasts, moulds [23] and bacteria [24]. Vanillin has also been reported to possess anticlastogenic, antimutagenic and antitumor properties and therefore it can be considered as a nutraceutical molecule [25]. Vanillic acid is also an intermediate in the production of vanillin from ferulic acid [26].

Recently, there has been an upsurge of interest to explore the antihyperglycemic, antihypertensive and antioxidant potential of natural products. Very few scientific reports are available on the antihypertensive and antioxidant effects of phenolic acids in diabetic hypertensive rats.

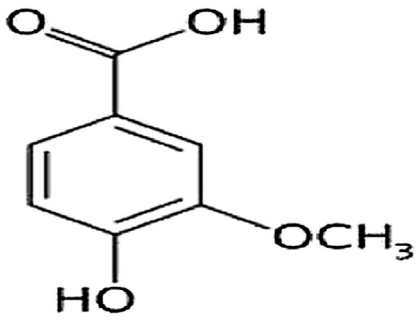

Fig. 1. Structure of vanillic acid.

Hence the present study was undertaken to assess the action of vanillic acid on lipid perioxidation and the status of the antioxidant defense system in control and high fat diet induced diabetic hypertensive rats.

2. Materials and methods

2.1. Chemicals

The chemicals used for the study were of analytical grade. Vanillic acid was purchased from Sigma Chemical Co. (USA). All other chemicals were purchased from Hi-media Laboratories Private limited. Mumbai.

2.2. Experimental animals

All experiments were performed using age and gender matched male Wistar rats. The rat were bred and obtained from the Annamalai University, Annamalai nagar. All the experiments were reviewed and comply with recommendation of the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India and the experimental protocol were approved by the Animal Ethical Committee of Annamalai University (vide no. 1059). The experimental rats were randomly assigned into four groups and maintained under controlled room temperature ($25 \pm 2\,^{\circ}C$) with relative humidity ($45 \pm 5\%$), on 12:12 h light dark cycle lighting. The rat were acclimatized to their environment for one week and provided with food and water *ad libitum* before the dietary intervention. At the start of the experiment, the experimental groups were fed with High fat diet (HFD), which comprised of sucrose (25%), beef tallow (50%) and rodent chow (25%). Sucrose, beef tallow were replaced by the cornstarch in control groups as considered as standard pellet diet and water *ad libitum*. The rats were maintained in accordance with the guidelines of the National Institute of Nutrition, Indian council of Medical Research, Hyderabad, India.

2.3. Induction of diabetic hypertension

To develop experimental diabetic hypertensive model, the Wistar rat were receive the HFD diet as described above for 12 weeks. The development of diabetic hypertension was confirmed by measuring the fasting plasma glucose level and systolic blood pressure (tail cuff method). Rat with plasma glucose level higher than 200 mg/dl (11.1 mmol/l) and systolic blood pressure higher than 135 mmHg were selected for continuation the present study up to 20 weeks.

2.4. Experimental design

The rats were randomized and divided into four groups (n = 6) as follow: Group 1 rats were fed standard pellet diet throughout the experimental period of 20 weeks and served as control; group 2 rats received vanillic acid with standard pellet diet for the last 8 weeks of the experimental period; group 3 rats received HFD throughout the experimental period of 20 weeks; group 4 rats received HFD throughout the experimental period of 20 weeks along with vanillic acid for the last 8 weeks (as in group 2) (Fig. 2).

Group 1 and group 2 rats received standard pellet diet, group 3and 4 received HFD for daily at standard intervals. Vanillic acid dissolved in vehicle solution (saline) and administered orally using an intragastric tube for a period of last 8 weeks. Body weight was measured weekly throughout the study. After 8 weeks of Vanillic acid treatment, experiments were terminated and observations were made. At the end of the experimental study the rats were