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High-dose chlorogenic acid induces inflammation reactions and oxidative stress injury in rats without implication of mast cell degranulation

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ABSTRACT

Ethnopharmacological relevance: Chlorogenic acid (CA) exits widely in those Chinese herbal injections that have antibacterial and antiphlogistic effects and belongs to the ethnopharmacological family of medicines. Chinese herbal injections containing high levels of CA have been reported to increase the adverse drug reactions, but the mechanism for which is still unclear. In this study, we investigated the mechanism of the CA derived adverse drug reactions.

Aim of the study: The present study was to explore the potential role of CA in initiating inflammatory reaction and the underlying mechanism.

Materials and methods: Male Wistar rats were treated with different dosages of CA for different time period. The variables examined included microcirculation by intravital microscopy, histology of ileum tissue, expression of adhesion molecules CD11b and CD18 on leukocytes by flow cytometry, myeloperoxidase activity and maleic dialdehyde content in ileum tissue by spectrophotometry, activity of superoxide dismutase and catalase in serum by ELISA, and expression of NADPH oxidase subunits by PCR and Western blot.

Results: High-dose CA increased the number of adherent leukocytes, generation of peroxides in the venular walls and induced albumin leakage from mesentery venules. High-dose CA induced changes also included an increase in maleic dialdehyde, myeloperoxidase, inflammatory cytokines and NADPH oxidase activities, and a decline in activity of superoxide dismutase and catalase.

Conclusion: High-dose, but not Low-dose CA induced inflammation reaction, and in this process an imbalance between oxidant and antioxidant mechanism may be involved, providing more information for better understanding the rationale behind the adverse effects of CA.

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1. Introduction

Chlorogenic acid (CA, Fig. 1) is widely distributed in the plant kingdom. Most Chinese herbal medicines with antibacterial, detoxifying, antiphlogistic and cholagogic effects contain CA, and CA is also commonly used as a characteristic marker for quality control in Traditional Chinese Medicine (Huang et al., 2010). However, Chinese herbal injections containing high levels of CA have been found to evoke increasing adverse drug reactions, such as pruritus, vomiting, asthma, diarrhea, shock, liver and kidney injury, and even death in clinical practice. The mechanisms for the adverse effects of CA have become a subject of increased interest in recent years, but little information is available to address the causes of these reactions.

CA, the ester formed between caffeic acid and quinic acid, being a secondary metabolite of phenylpropanoid, is produced via the shikimate pathway used in the aerobic respiration of plants. CA is an abundant ingredient in coffee and present in many foods, such as sweet potatoes and apples (Padda and Picha, 2007; Tang and Liu, 2008). CA is known to display a multiple pharmacologic effects, including antibiotic, antiviral (Ozcelik et al., 2011), anticancer (Lambert et al., 2005), and hypoglycemic activity (Bassoli et al., 2008), and has attracted considerable attention due to its

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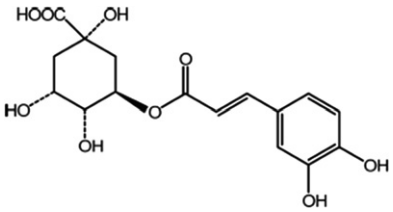

Fig. 1. Chemical structure of chlorogenic acid.

antioxidative activities (Gugliucci et al., 2009; Roche et al., 2005). However, an antioxidant might become a prooxidant which accelerates lipid peroxidation and/or induces DNA damage under special conditions (Azmi et al., 2005; Fukuhara et al., 2006; Lee and Lee, 2006; Sakihama et al., 2002). This turnover is likely to occur in CA as well (Fan et al., 2009). In addition, study reported that CA-induced reactive oxygen species (ROS) can induce apoptosis by disrupting mitochondrial membrane potential and activating caspases (Rakshit et al., 2010). It is postulated that it is the prooxidant action of CA that is responsible for some of its pharmacologic activities, including anticancer (Zheng et al., 2008). Though the allergenicity has always been accepted as the cause responsible for the adverse effects of CA (Freedman, 1964a, b), question remains in this field (Layton et al., 1963; Layton et al., 1968). Allergenicity is characterized by hyperpermeability of microvessels, involving a range of insults, such as endothelial cell injury, enhanced adhesion of leukocytes, macromolecular efflux, production of oxygen radicals, and mast cell degranulation (Yuan et al., 2009; Han et al., 2001, 2007, 2009). It is not clear at present, however, which insult(s) is (are) implicated in the adverse effect induced by high-dose CA.

In the present study, by administration of CA at a dose high enough to induce adverse effect, we explored the potential role of the expression of adhesion molecules on leukocytes, leukocyte adhesion to venules, oxidative stress and mast cell degranulation in CA- elicited albumin leakage and inflammation.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 200–220 g were obtained from the Animal Center of Peking University Health Science Center (Beijing, Certificate No. SCXK 2006-0008). The rats were housed in cages at temperature 22 ± 2 °C and humidity $40 \pm 5\%$ under a 12-hour light/dark cycle, and received standard diet and water ad libitum. The rats were fasted for 12 h before the experiment. The investigations conformed to the EU adopted Directive 2010/63/EU and Guide of Peking University Animal Research Committee. Experiment protocols were approved by Peking University Biomedical Ethics Committee Experimental Animal Ethics Branch (LA2011-38).

2.2. Experimental groups and drug administration

Rats were randomly assigned to weight-matched groups. Rats were anesthetized by intramuscular injection with compound anesthetic (Chloral Hydrate 4.25 g, $MgSO_4$ 2.12 g, pentobarbital sodium 0.89 mg, EtOH 14.25 ml, 1, 2-propylene glycol 33.8 ml, and distilled water 51.95 ml; 3 ml/kg BW), and saline or CA was continuously infused via the left jugular vein catheter. CA (Sigma Chemical Co., St Louis, MO, USA) was dissolved in 0.9% NaCL, and administrated at 0.336 mg/kg body weight (low dose), 1.68 mg/kg body weight (middle dose) or 7 mg/kg body weight (high dose) at a speed of 8 ml/kg/h within 1 h. We chose 0.336 mg/kg body weight as a low dose because it is an average dose for most commonly used Chinese herb medicine injection, and no adverse effect has been reported at this dose. The dose 7 mg/kg body weight is 5-fold higher than that recommended in its instruction of Qingkaling injection, a Chinese herb medicine injection, and most reported adverse effects were found to occur at around this dose (Wang and Zhang, 2009). The dose 1.68 mg/kg body weight was selected as a middle dose between the two dosages. The animals in Control group received equivalent volume of saline within the same period of time. In one series of experiments, the animals were administrated with drug or saline only once, and then subjected to assessment of various parameters within 2 h. In a separated series of experiments, the animals were administrated with drug or saline for 3 times, once a day, and then underwent subsequent experiments. In another separated series of experiments, the animals were administrated with drug or saline for 7 times, once a day, and subjected to the concerning examinations. The number of animals for different experimental groups is shown in Table 1.

2.3. Microcirculatory observation

The surgical procedure was performed as previously described (Wang et al., 2010a). Rats were anesthetized by intramuscular injection of 20% urethane (1 ml/100 g BW). The abdomen was opened through an incision of 25–30 mm in length. The ileocecal portion of the mesentery (10–15 cm caudal) was gently drawn out, exteriorized, and mounted on a transparent plastic stage designed for the rat. The mesentery was kept warm and moist by continuous superfusion with saline solution at 37 °C. The mesenteric microcirculation was observed under an inverted microscope (DM-IRB Leica, Cologne, Germany) through a x20 objective lens. The mesentery was transilluminated with a 12-V, 100-W, direct-current-stabilized light source. The microscopic images were obtained using a color video camera (Jk-TU53H, Toshiba, Tokyo, Japan) mounted on the microscope, and the image was transmitted onto a monitor (J2118A, TCL, Huizhou, China). The images were recorded with a Digital Video Disk videocassette recorder (DVR-R25, Malata, Xiamen, China). A single unbranched venules (30–50 μm in diameter; 200 μm in length) were selected for study (Wang et al., 2010a).

Microcirculation examinations initiated after 10 min baseline observation. Adherent leukocytes were defined as cells that attached to the same site for more than 10 s as determined from a replay of the video images. The number of adherent leukocytes along venules (30–50 μm in diameter, 200 μm in length) randomly selected from the videotape images was counted at baseline (before infusion), and 60 min, 120 min and 3 d after infusion and expressed as the number per 200 μm of venule length (Wang et al., 2010a).

To evaluate albumin leakage across mesenteric venules, animals were intravenously injected with 50 mg/kg body weight of FITC-labeled bovine serum albumin (Sigma Chemical Co., St Louis, MO, USA). Ten min thereafter, the venules were observed under an inverted fluorescence microscope (DM-IRB, Leica, Cologne, Germany) with irradiation by an excitation light (455 nm). The image was recorded at baseline (before infusion), and 60 min, 120 min and 3 d after infusion. The fluorescence intensity of FITC-albumin inside the lumen of selected venule (Iv) and in an identical area of perivenular interstitium in vicinity (Ii) was measured. The ratio of Ii/Iv was calculated and compared with the baseline as an indicator of albumin leakage (Wang et al., 2010a).

The oxidant-sensitive fluorescent probe dihydrorhodamine 123 (DHR; Molecular Probes, Eugene, OR, USA) was topically applied to the mesenteric surface (10 μmol/L) 5 min before observation, to monitor oxidant stress in the venular walls. The fluorescence image was recorded at baseline (before infusion), and 60 min, 120 min and 3d after infusion with an inverted

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