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Intervention effect and mechanism of curcumin in chronic urinary tract infection in rats

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ABSTRACT

Objective: To analyze the invention effect of curcumin on chronic urinary tract infection in rats and explore its possible mechanism of action.

Methods: The experimental animals were randomly divided into three groups, normal, model and curcumin group. Chronic urinary tract infection models were built for model group and curcumin group by injecting coliform fluid into the cavity of bladder. From the first day of modeling, rats in the curcumin group were injected with 150 mg/kg curcumin, while rats in normal group and model group were given no other treatment. The treatment lasted for 14 d. The white blood cell counts in blood and urine, bacterial colony count in urine and renal tubular functional indexes of rats in all groups at day 1, 7, and 14 after treatment were detected. Urine β2-microglobulin (β2-MG), urinary N-acetyl-β-D glucosaminidase (NAG) levels were used to detected the inflammatory cytokines in serum after treatment including the contents of IL-6, IL-8, IL-10 and monocyte chemoattractant protein-1 (MCP-1), and real-time PCR was employed to determine the expression of mRNA of toll-like receptor 2 (TLR-2) and TLR-4 in renal tissues and bladder tissues of all groups after treatment.

Results: The white blood cell counts at day 1 and 7 after treatment in rats of model group and curcumin group were significantly higher than those of normal group at the same time points, while the white blood cell counts of the curcumin group were significantly lower than those of model group ($P < 0.05$). The urine white blood cell counts in rats of model group at day 1, 7 and 14 were all significantly higher than those of normal group at the same time points; those in the curcumin group were significantly lower than those of the model group at day 1, 7 and 14 at the same time points ($P < 0.05$). The bacterial colony counts of urine in rats of model group and curcumin group at day 1, 7 and 14 were all significantly higher than those of normal group at the same time points, while the counts of curcumin group were significantly lower than those of model group at the same time points ($P < 0.05$). Levels of urine β2-MG, NAG, IL-6, IL-8, IL-10, MCP-1 and expression of TLR2 mRNA and TLR4 mRNA in renal and bladder tissues in rats of model group were significantly higher than those of the normal group, while these variables of the curcumin group were significantly higher than those of the normal group but lower than those of model group ($P < 0.05$).

Conclusions: Curcumin can significantly improve the symptoms of chronic urinary tract infections, protect renal tubular function, and also decline inflammatory responses by influencing the expressions of TLR2 mRNA and TLR4 mRNA so as to exert its curative effect on chronic urinary tract infections.

1. Introduction

Urinary tract infection is a common infectious disease in the urinary system caused by pathogens invading the urinary tract and leading to urinary tract inflammatory lesions. Clinically, urinary tract infection mainly includes urethritis, cystitis and pyelonephritis [1,2]. Epidemiological data have shown that the prevalence rate of the disease is about 0.9%, and it is more prevailing in female group than males [3,4]. Urinary tract

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infection is common in women of child-bearing age and rural woman. Since urinary tract infection is characterized by repeated outbreak, long disease course, protracted and refractory treating process and difficulty for treatment, a serious of severe complications can occur with the development of the disease with poor prognosis [5,6]. Although antibiotics can alleviate the conditions to a certain extent, they cannot decline the recurrence rate and improve the prognosis of the diseases. In particular, with the application of the broad-spectrum antibiotics in recent years, pathogens of urinary tract infection have shown different degrees of antibiotic resistance, which, as a result, affects the therapeutic effect [7]. At present, it is rather difficult to treat urinary tract infection in clinic. An in-depth understanding of the pathogenesis of this disease is of great clinical significance for seeking new approaches and therapeutic drugs to prevent and treat the disease.

Chronic urinary tract infection is a kind of chronic inflammatory infectious disease. Studies have reported that many inflammatory cytokines are highly expressed in serum of patients with chronic inflammatory infectious disease [8–10]. Toll like receptor, a kind ofltrans-membrane receptor of the pathogen-associated molecular pattern, can cause inflammatory chain reaction [11]. In addition, it is found that toll like receptor has something to do with the activation of innate immunity [12] and identification of pathogenic bacteria [13]. Curcumin is the major component of *Carcuma* longa. It is a plant polyphenol with broad biological activities including immunoregulation, anti-inflammation and so on [14,15]. Curcumin has been used in clinic to treat multiple inflammatory diseases including ulcerative colitis [16] and has achieved significant efficiency. However, no report on the intervention effect of curcumin on chronic urinary tract infection has been found. Therefore, this study aimed to observe the effect of curcumin on chronic urinary tract infection and explore its possible mechanism of action by establishing rat models with chronic urinary tract infection given curcumin intervention.

2. Materials and methods

2.1. Materials

2.1.1. Reagents and drugs

Curcumin was made into 40 mg/mL suspension by Sinopharm Chemical Reagent Co. Ltd. (batch number: 8239401). The 7020 automatic biochemical analyzer (Hitachi, Japan), BCC-3000B blood-cell counter (Shanghai Huanxi Medical Instrument Co. Ltd., China), and mission U500 urine analyzer (ACOM, Hangzhou) were employed. Interleukin (IL)-6, IL-8, IL-8, and monocyte chemoattractant protein-1 (MCP-1) reagents were all purchased from Boster, Wuhan; iMark ELIASA was from BIO-RAD, USA. ABI7500 real time PCR was from Applied Biosystems, USA. The related primers were compounded by Norman Biological Technology, Nanjing. Amplification reaction kits, Trizol kits and Trizol tissue lysate were all bought from BD, USA.

2.1.2. Pathogenic bacteria

Standard *Escherichia coli* (ATCC25922) (*E. coli*), bought from the Pathogen Biology Laboratory of Experimental Center, College of Lab Medicine, Hebei North University, were made into 300 million/mL *E. coli* solution for standby application.

2.1.3. Experimental animals

Healthy SD rats (160–200 g) were bought from Hebei Experimental Animal Center with production license of SCXK (Yi) 2008-1-003. Animal feeding and the subsequent experiments were all done in Hebei Experimental Animal Center. The feeding conditions included natural sunlight, free diet, 20–23 °C room temperature. Feeding and the subsequent experiments were all met the requirements of Manipulative Technique for the Care and Use of Laboratory Animals. The study was approved by the Ethics Committee of our hospital.

2.2. Methods

2.2.1. Groups and modeling

The experimental animals were randomly divided into three groups: normal group, model group and curcumin group. Each group had 5 males and 5 females. Animals were supplemented if the experimental animals died halfway. Chronic urinary tract infection models were built for the model group and curcumin group. Detailed procedures were described as follows: rats were forbidden to drink for 24 h, and then given urethane for intraperitoneal anesthesia. Lower abdominal hairs were removed after fixing their four limbs. A 3 cm incision was made in the middle of the abdomen to expose the abdominal cavity. Then, 0.1 mL *E. coli* solution was injected intravesically. The ureter was ligatured and the incision was sutured. The abdominal cavity was closed. The experimental animals then drank and eat normally. Twenty-four hours later, the ligature string was removed.

2.2.2. Drug administration

From the first day of modeling, rats in the curcumin group were injected with 150 mg/kg curcumin, while rats in the normal group and model group were given no other treatment but free access to forage and drinking water. The treatment lasted for 14 d.

2.2.3. Sample collection and management

After the last drug administration, abdominal aorta blood and the 24 h urine were collected. Rats were sacrificed, and their mucosal tissues of the trigone of urinary bladder and the left pelvis were taken out and fixed with formalin, and cryopreserved for further detection.

2.2.4. Routine blood and urine tests and colony counts

Automatic blood-cell counter and urine analyzer were used to measure the white blood cell counts in blood and urine and colony counts in urine, respectively.

2.2.5. Detection of renal tubular function

Automatic biochemical analyzer was applied to urine β2-microglobulin (β2-MG) and urinary N-acetyl-β-D glucosaminidase (NAG). NAG was determined by glucoside, and β2-MG was detected by radioimmunoassay.

2.2.6. ELISA

ELISA was used to test the contents of serum inflammatory cytokines IL-6, IL-8, IL-10 and MCP-1. The first step was to establish standard curve. Next step was to dilute the sample. Then, the tested sample was added. After the plate was washed by cleaning mixture and dried by filter paper, biotinylated

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