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EXPERIMENTAL STUDY

Effect of Qilongtoutong granule on calcitonin gene-related peptide, beta-endorphin, serotonin, dopamine, and noradrenalin in migraine model rats and mice

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Abstract

OBJECTIVE: To study the effect of Qilongtoutong granule (QLTT) on plasma calcitonin gene-related peptide (CGRP), beta-endorphin (β-EP), 5-HT, dopamine (DA), noradrenalin (NE), and blood viscosity in migraine model rats and mice.

METHODS: Both the acute blood stasis model group and nitroglycerin-induced migraine model group included 60 Sprague-Dawley rats. The reserpine-reduced model group had 60 Kunming mice. Rats from each test were grouped into normal control group, model group, Zhengtian pill (ZTP) group, and high, moderate, or low-dose QLTT groups. In the acute blood stasis model test, after gavage for 7 days, rats were given 0.8 mL/kg adrenaline hydrochloride subcutaneously twice, and kept in ice water for 5 min. After fasting for 12 h, rats were anesthetized and blood samples were collected for detection of blood viscosity. In the nitroglycerin-induced migraine group, after gavage for 7 days, rats were intraperitoneally injected nitroglycerin (10 mg/kg), and 4 h later, blood samples were collected from postcava for measuring the plasma CGRP and β-EP levels. In the reserpine-reduced model test, except the normal control group, mice were administered reserpine (0.25 mg/kg, i.h.) for 9 days. Mice received intragastric administration from the third day to the ninth day. One hour after the last gavage, blood and brain tissue samples were obtained. Then, blood clotting time and the contents of neurotransmitters were determined.

RESULTS: QLTT- (3.6, 1.8, and 0.9 g/kg) and ZTP-treated rats had lower blood viscosity than that in model rats under different shear rates ($P<0.01$). QLTT- (3.6, 1.8 g/kg) and ZTP-treated rats had significantly lower plasma CGRP levels and higher plasma β-EP levels than those in model rats ($P<0.01$). QLTT treatment at dose of 0.9 g/kg had lower plasma CGRP levels as well ($P<0.05$). QLTT- (5.2, 2.6 g/kg) and ZTP-treated mice had longer blood clotting time than that in model mice ($P<0.01$). QLTT- (2.6 g/kg) and ZTP-treated mice had higher plasma serotonin (5-HT) levels than those in model mice ($P<0.05$).

CONCLUSION: QLTT-treated animals had lower plasma CGRP level, higher plasma β-EP, 5-HT, higher brain tissue 5-HT, NE, DA levels, and lower blood viscosity than those in the migraine model animals.

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Key words: Migraine disorders; Calcitonin gene-related peptide; Beta-endorphin; Medicine, Chinese traditional; Qilongtoutong granule

INTRODUCTION

Migraine is a common disease that adversely affects quality of life.[1] However, few migraine medications achieve an effective rate over 50% and side effects limit their use.[2] Therefore, it is clinically significant to seek new drugs for migraine. A Chinese medicine formula for the treatment of migraine, Qilongtoutong granule (QLTT), has been used in clinic over 50 years.

According to the theory of Traditional Chinese Medicine (TCM), the stagnation of *Qi* and blood may bring about pain. Therefore, activating blood, expelling blood stasis, and dredging collaterals are the principles for migraine management. Research indicates that calcitonin gene-related peptide (CGRP) is responsible for neurogenic inflammation and vasodilatation of the cranial vessels in migraine pathophysiology.[3] Some scholars found that beta-endorphin (β-EP), by modulating the release of sympathetic transmitters, played a role in the pathogenesis of migraine.[4] Research also showed that a fall of serotonin (5-HT) in plasma and brain tissue was a specific feature of migraine attacks.[5] Additionally, a study showed that anomalies in the metabolism of glutamate, γ-aminobutyric acid, and those that govern pain and vegetative functions, such as 5-HT, dopamine (DA), and noradrenalin (NE), constituted the phenotypical biochemical cause of the migraine.[6] Based on these studies, an acute blood stasis model was used to assess the effect of QLTT on activating blood and expelling blood stasis. A nitroglycerin-induced migraine model was used to investigate the efficacy of QLTT on plasma CGRP and β-EP, and a reserpine-induced low 5-HT model was employed to explore the effect of QLTT on plasma 5-HT concentrations and the contents of 5-HT, DA, and NE in brain tissue.

MATERIALS AND METHODS

Preparation of QLTT

QLTT was manufactured in the pharmacy department of Chinese People's Liberation Army General Hospital (Beijing, China). It was prepared with 12 medicinal herbs: 2 parts Huangqi (*Radix Astragali Mongolici*) and Baishao (*Radix Paeoniae Alba*); 1.5 parts Danggui (*Radix Angelicae Sinensis*), Gegen (*Radix Puerariae Lobatae*) and Jili (*Fructus Tribuli*); 1.2 parts Chuanxiong (*Rhizoma Chuanxiong*), Juhua (*Flos Chrysanthemi*) and Dilong (*Pheretima Aspergillum*); and 1 part stir-frying Gancao (*Radix Glycyrrhizae*), Ruxiang (*Olibanum*), Moyao (*Myrrh*), and Tianma (*Rhizoma Gastrodiae*). Herbs were purchased from Anguoshi Changda Chinese Herbal Pieces Co., Ltd. (Hebei, China). All herbs met the standards of the Chinese Pharmacopoeia (2010 Edition, Volume I).[7] Dilong (*Pheretima Aspergillum*) and Moyao (*Myrrh*) were ground into a fine powder and filtered through a 100 mesh. Jili (*Fructus Tribuli*) and Tianma (*Rhizoma Gastrodiae*) were pulverized into a coarse powder and decocted with the other eight herbs three times. The herbs were decocted with an eight-fold volume of water for 1.5 h, then six-fold and four-fold volumes of water for 1 h. The three decoctions were filtered, mixed together and concentrated under reduced pressure to a thick paste with relative density 1.13 to 1.15 (50℃). The thick paste was dried at 80℃ and ground into a fine powder with 100 mesh. This powder was then mixed with the Dilong (*Pheretima Aspergillum*) and Moyao (*Myrrh*) powder. Sucrose and dextrin in the ratio of 2∶1 were also added. After mixing evenly, all herbs were dried and packed. The wet granulation technique was employed to prepare QLTT and the yield of the extract was about 20%.

Reagents and apparatus

The following reagents and apparatus were used in the experiment: Zhengtian pill (ZTP, China Resources Sanjiu Medical & Pharmaceutical Co., Ltd., Shenzhen, China), adrenaline hydrochloride injection (Tianjin Pharmaceutical Group Xinzheng Co., Ltd., Tianjin, China), nitroglycerin injection (Beijing Yimin Pharmaceutical Co., Ltd., Beijing, China), trichloroacetaldehyde hydrate (Sinopharm Chemical Reagent Co., Ltd., Shanghai, China, analytical reagent), reserpine injection (Guangdong Bangmin Pharmaceutical Co., Ltd., Jiangmen, China), 5-Hydroxytryptamine hydrochloride (National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China), noradrenaline bitartrate (National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China), dopamine hydrochloride (National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China), evacuated blood collection system (Greiner Bio-One GmbH, Krems munster, Austria), Rheogeniometer SA-7000 (Beijing Sicceeder Technology Development Co., Ltd., Beijing, China), CGRP RIA kit (Beijing Huaying Biotechnology Research Institute, Beijing, China), β-EP RIA kit (Beijing Huaying Biotechnology Research Institute, Beijing, China), phosphoric acid (Sinopharm Chemical Reagent Co., Ltd., analytical reagent, Shanghai, China), sodium heptanesulfonate (Sinopharm Chemical Reagent Co., Ltd., analytical reagent, Shanghai, China), acetonitrile (Fisher Scientific, Langenselbold, Germany, spectrographic grade), Agilent Technologies Series 1200 system (Agilent, Santa Clara, CA, USA), mouse 5-Hydroxytryptamine ELISA Kit (Beijing Aike Boya Biotechnology Co., Ltd., Beijing, China), and ELISA plate reader (Multiskan Ex Primary EIA V.2.3, Thermo, Vantaa, Finland).

Animals

A total of 120 Sprague-Dawley rats (60 males and 60 females, 6-8 weeks old, 180-220 g, SPF) and 60 Kun-

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