Journal of Traditional Chinese Medical Sciences (2018) 5, 72—79

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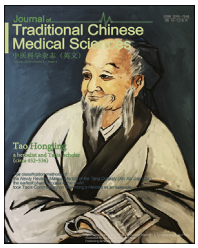

Changes of respiratory function on urine volume, renal AQP1, and AQP2 in mice with bronchial asthma and effects of lung-diffusing herb *Platycodon grandiflorus* (JACQ.) A.DC.

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Received 15 December 2017; received in revised form 9 January 2018; accepted 9 February 2018
Available online 17 March 2018

KEYWORDS
Bronchial asthma;
The lung controlling breathing;
Regulation of water pathways;
Platycodon grandiflorus (JACQ.) A.DC.;
Aquaporin

Abstract *Objective:* To observe the effect of respiratory-function changes on urinary output and expression of aquaporin (AQP) in kidney tissue in bronchial asthma (BA) model mice. To explore the correlation between the lung controlling breathing and the lung regulating the waterways, and observe regulation by the lung-diffusing herb platycodon root (*Platycodon grandiflorus* (JACQ.) A.DC.).
Methods: Forty-five healthy female Balb/c mice were divided randomly into normal, model and platycodon root groups. The BA model was replicated by complex sensitization and stimulation with ovalbumin (OVA). Changes in airway resistance were detected using an AniRes2005 system, and 24-hour urine output collected by metabolic cages. Histopathologic changes in the lung and kidney were observed by H&E staining. Expression of the mRNA of AQP1 and AQP2 was detected by reverse transcription-polymerase chain reaction, immunohistochemistry, and immunofluorescence.
Results: Compared with the normal group, airway resistance in the inspiratory phase intensified in the model group ($P < .01$). Following the pathologic changes in lung tissue, but no significant change in kidney tissue, 24-hour urinary output decreased significantly ($P < .05$), and levels of AQP1, AQP2 and their mRNA increased significantly in the model group ($P < .01$). Compared with the model group, airway resistance in the inspiratory phase was weakened

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Peer review under responsibility of Beijing University of Chinese Medicine.
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https://doi.org/10.1016/j.jtcms.2018.02.005

($P < .01$). The urinary output increased ($P < .05$), pathologic changes in lung tissues decreased, and renal expression of AQP1, AQP2 and their mRNA decreased significantly ($P < .01$) in the platycodon root group.

Conclusion: Changes in respiratory function in BA model mice can affect how the lung regulates water pathways. Platycodon root diffusing the lung can ameliorate the respiratory-function and pathologic changes in the lung tissues of BA model mice, but also regulate urinary output and renal expression of AQP1 and AQP2.

Introduction

Bronchial asthma ("asthma"; BA) is a heterogeneous disease characterized by chronic airway inflammation with the respiratory symptoms of wheezing, shortness of breath, chest tightness, and coughing, with variable airflow limitation and intensity varying with time.[1] The worldwide population of asthma sufferers has been estimated to be ≈ 300 million, with ≈30 million in China.[2] Epidemiologic and toxicological studies have shown that exposure to airborne pollutants is associated with the morbidity or mortality of respiratory diseases, cardiovascular diseases, allergic diseases, and diabetes mellitus.[3–7] Substantial evidence suggests that particulate matter can aggravate an acute exacerbation of asthma (and even cause an asthma attack).[4,8]

Asthma is a common respiratory disease, and may also have effects on other organs apart from the lung. In an acute (especially a severe) attack of asthma, the patient loses a large amount of water due to mouth breathing and hyperventilation. This leads to the increased evaporation of respiratory air, profuse sweating, and difficulty in drinking water, and so the patient presents with orthopnea, dry lips, profuse sweating, cold skin and oliguria.[9]

Traditional Chinese medicine (TCM) theory states that the lung governs breathing and regulates the water pathways. Physiologically, the normal respiratory function of the lungs is accomplished by promoting the distribution and discharge of water based on the diffusion and purification of the lungs. In disease, blockage of the lung qi and failure to purify and descend affects qi transformation. Little research has been done on the effects of water metabolism in asthma, and we wished to explore it based on TCM theory.

In TCM, there is a typical treatment method named "lifting the lid from the teapot frees the flow of qi and regulates the water pathways by diffusing the lung qi to promote smooth urination".[10] *Platycodon grandiflorus* is a species of herbaceous flowering perennial plant of the family Campanulaceae. The root of this plant (*Platycodon grandiflorus* (JACQ.) A.DC.) has a bitter and acrid flavor. With its characteristics of diffusion and ascent, this herb can clear the throat, rectify qi, unbind the chest, and carry other herbs upwards. Platycodon root is used widely in water-promoting formulas for the treatment of water-metabolism disorders such as postpartum anuresis due to its significant effects on diffusing the lung and promoting urination.[11]

Aquaporins (AQPs) are a family of cell-membrane proteins that mediate the rapid transmembrane transport of water molecules. Their main function is to regulate water balance in the body, and they have a key role in the fluid balance within organs. Scholars from China and overseas have shown that AQPs have important roles in the water metabolism of the kidney.[12]

Aquaporin 1 (AQP1) was the first AQP to be discovered and identified, and is expressed in lung and kidney tissues.[13] It is closely related to the metabolism of water and body fluids. Studies have shown that urine volume is increased in AQP1 knockout mice.[14] It is believed that the lung, spleen, and kidney are involved in water regulation in TCM studies. AQP1 is one of its molecular bases of this hypothesis. Herbs with the actions of tonifying and boosting kidney yang can up-regulate AQP1 gene expression.[15] This AQP1 expression continues to be down-regulated in the lung tissue of rats with chronic obstructive pulmonary disease as identified by cold-rheum accumulation in the lung. Also, yang-warming and rheum-dissolving formulas can up-regulate AQP1 expression in lung tissue.[16]

Aquaporin 2 (AQP2) is involved in the regulation of water balance in renal collecting tubes. AQP2 is the main molecular actor for the renal reabsorption of water and urine concentration to maintain water balance in the body. Some studies have indicated that *Yixintai* granules can ameliorate chronic heart failure, possibly through down-regulation of the mRNA and protein expression of AQP2 in the renal medulla, and increasing the urine volume.[17]

In the present study, we used a single Chinese herb, the platycodon root, with its actions of diffusing the lung, in BA model mice. We observed its effects on expression of AQP1 and AQP2 in BA model mice. We explored the close relationship between the regulation of breathing and regulation of the water pathways of the lung. In this way, we wished to provide experimental evidence for the clinical application of "lifting the lid from the teapot".

Materials and methods

Ethical approval of the study protocol

All experimental procedures were undertaken in accordance with the *Guidelines for the Care and Use of Laboratory Animals* (National Institutes of Health, Bethesda,