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Short Review Open Access

The Role of Orexin in the Effect of Electroacupuncture on Inflammatory Cytokines and Respiratory Regulations in a Rat Model of Smoke Induced Chronic Obstructive Pulmonary Disease: A Short Review

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Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation [1,2]. By 2020, COPD will rank third as the cause of death worldwide (it is sixth place in 1990), while the social burden of COPD will rank fifth (it is twelfth place in 1990). 90% of patients with COPD are smokers in Western countries, thus smoking has become one of the most important pathogenic factors in this disease [3-5]. COPD is thought to be caused by inflammation induced by inhaled smoke and particulates, conducting structural changes in airways and alveoli, resulting in airflow limitation. The pathology of COPD involves small airways and lung parenchyma, with chronic inflammation conducting luminal obstruction, thickening of the airway wall by increased deposition of matrix molecules and proliferation of mesenchymal cells, and narrowing of the airway by fibrosis, causing a decrease in lung function [1,6].

There are some different therapies for COPD. The anti-inflammatory therapy is one choice [7]. Targeting oxidative stress with antioxidants is likely to be beneficial in the treatment of the disease [8]. Acupuncture has been used as a clinical treatment for various diseases in traditional Chinese medicine for a long time including COPD. Although acupuncture can improve exercise capacity, respiratory function and respiratory muscle strength in patients with COPD its mechanisms are still unclear [9,10].

We first found that electroacupuncture (EA) could reduce lung injury in a COPD rat model, and the beneficial effects may be related to down-regulation of inflammatory cytokines and oxidants. And our further results suggested EA at Zusanli and Feishu improved lung function of rats with COPD and had an anti-inflammatory effect, which may be related to down regulation of OXA and its receptors [11-15].

The anti-inflammatory and antioxidant effects of EA

In our first paper we established the COPD model using male Sprague-Dawley rats exposed to cigarette smoke. The rats were randomly divided into four groups (control, sham, COPD, and COPD plus EA), and COPD model was evaluated by measuring pulmonary pathological changes and lung function. EA was applied to the acupuncture point Zusanli (ST36) for 30 min/d for 14 d in sham and COPD rats. Bronchoalveolar lavage fluid (BALF) was used to measure levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and malonaldehyde (MDA).

Compared with the control rats, COPD rats had significant changes in lung resistance (RL) and lung compliance (CL) (both $P<0.01$), bronchi and bronchiole airway obstruction, and levels of MDA, TNF-α, and IL-1β. Compared with the COPD rats, the COPD plus EA rats had decreased RL and increased CL, and reduced bronchi and bronchiole airway obstruction, while levels of TNF-α, IL-1β, and MDA in BALF were lowered. However, TNF-αand IL-1β levels of the EA group rats remained higher than those of the control group. EA at ST36 can reduce lung injury in a COPD rat model, related to down-regulation of inflammatory cytokines. The clinical benefit of EA may from the anti-inflammatory and antioxidant effects [11].

The role of orexin in the mechanism of EA therapeutic action

Acupuncture at Zusanli (ST36) has anti-inflammatory and antioxidant effects but the mechanism of acupuncture's therapeutic action is not known. Neuropeptide orexins (OXs), discovered by Sakurai et al in 1998, are synthesized by the neurons in the lateral hypothalamic area of rats, and can be alternatively spliced into OXA and OXB [16]. OX neurons are located in the hypothalamus, but their fibers project to multiple brain sites, including the medullary respiratory center. Microinjection of OX can cause phrenic and hypoglossal nerve discharges, suggesting that OX is involved in the central regulation of respiratory activity [17,18]. We previously demonstrated respiratory activity in COPD rats with relatively high expression of OXA and its receptors in hypothalamus and medulla [19].

Orexin A and B levels in the lung tissue were detected by enzyme-linked immunosorbent assay. OX receptor mRNA levels and immunopositive cells were assessed with real-time polymerase chain reaction and immunohistochemical methods, respectively. The relationships among lung function, cell factors, and OX levels were analyzed by Pearson correlation analyses.

Compared with the control group, there were obvious increases in orexin A level, mRNA expressions of OX 1 type receptor (OXR1) and OX 2 type receptor (OXR2) in lung tissue; the integrative optical densities (IODs) of both receptors were greater in the COPD group. Orexin A, but not orexin B, levels in lung tissue also decreased, as did mRNA expression of OX1R and OX2R in lung tissue. Receptor IODs were also reduced after EA treatment. Furthermore, orexin A levels and ratio of forced expiratory volume in 0.3 s to forced vital capacity were strongly negatively correlated, and orexin A was positively correlated with TNF-α and IL-1β [12].

So our results suggest that EA could regulate the orexin levels in the lung tissue and play the therapeutic action of anti-oxidant and anti-inflammation.

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