Clinical application of ghrelin for chronic respiratory failure

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Abstract. Chronic respiratory failure, which is often caused by chronic obstructive pulmonary disease, chronic lower respiratory tract infection, or interstitial pneumonia, often leads to cachexia with disease progression. Patients who have chronic respiratory failure with cachexia exhibit increased morbidity. Although cachectic status is an important clinical problem, there are no effective therapies for cachexia. Ghrelin has various effects, including increasing food intake, attenuating sympathetic nerve activity, inhibiting inflammation, increasing cardiac output, and controlling fat utilization. These effects of ghrelin are ideal targets for the treatment of severely wasting chronic respiratory disease. In a few clinical studies, including a small randomized controlled trial, ghrelin administration to cachectic patients with chronic respiratory failure improved exercise tolerance, dyspnea, and appetite. The patients in these studies gained muscle mass and weight. In another study of chronic lower respiratory tract infection with cachexia, ghrelin suppressed airway inflammation by decreasing neutrophil accumulation in the airway, resulting in improvements in oxygenation and exercise tolerance. Although further clinical investigations are needed to clarify its usefulness, ghrelin is expected to become a novel therapy for cachectic patients with chronic respiratory failure.

Key words: Ghrelin, Chronic respiratory failure, Cachexia

PATIENTS with chronic respiratory failure usually have deficiencies in exchange of carbon dioxide for oxygen, resulting in low oxygen or high carbon dioxide levels in the blood. Chronic obstructive pulmonary disease (COPD), chronic bronchitis, and idiopathic interstitial pneumonia usually lead to chronic respiratory failure. When respiratory diseases with chronic respiratory failure progress to advanced stages, cachexia often occurs [1]. Cachexia is a condition that is often associated with appetite loss, increased metabolic rates, and physical and muscle exhaustion. A respiratory disease with cachexia worsens the patients’ quality of life and prognosis [1, 2].

Although cachexia is a serious problem in clinical practice, we do not currently have any effective treatments for this condition. However, research on the effects of ghrelin has resulted in the development of approaches to treating cachexia. Ghrelin has various physiological effects, including increased food intake and muscle mass, suppression of pro-inflammatory cytokine production, and regulation of energy metabolism. These are appropriate targets for the treatment of cachexia in association with respiratory failure. Here, we describe the clinical application of ghrelin for the treatment of cachexia with chronic respiratory failure.

Pulmonary cachexia and ghrelin

The hallmarks of COPD are a history of smoking, cough with sputum, and dyspnea upon effort. COPD patients exhibit two major pathologic mechanisms: emphysema, caused by alveolar destruction, and bronchitis, caused by airway inflammation. Airway inflammation associated with COPD causes airflow limitation, which is not fully reversible. The inflammation associated with COPD usually progresses to significant respiratory symptoms, including cough, sputum, and dyspnea on effort. In addition to the respiratory symptoms, patients with advanced COPD often have severe symptoms such as appetite loss, weakness, and skeletal muscle wasting. These are characteristics of cachexia, which is due to a catabolic state, increased muscle apoptosis, and muscle disuse [3]. The cachexia associated with COPD is thought to be caused by increased production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin
Patients with severe COPD who are experiencing chronic respiratory failure often have cachexia, and such patients have much higher mortality than COPD patients without cachexia [5]. Increased growth hormone (GH) release, up-regulation of appetite, and energy metabolism regulation, all of which are physiological effects of ghrelin, are predicted to ameliorate the serious condition of cachectic patients with advanced COPD.

A multicenter, randomized, double-blind, placebo-controlled clinical trial of ghrelin administration for 33 COPD patients was conducted by Miki et al. [6]. The target patients of this study were severe and cachectic COPD patients with a body mass index less than 21. Enrolled patients were randomly assigned ghrelin (2 μg/kg, twice daily) or saline administration for three weeks. Muscle exercise training of lower limbs using electromechanically braked cycle ergometers and pulmonary rehabilitation were planned for all enrolled patients. A remarkable improvement of St. George’s Respiratory Questionnaire scores, a health-related quality of life (QOL) questionnaire for patients with asthma and COPD, was observed in the ghrelin treatment group in comparison with the placebo group. In addition, exercise tolerability, which was evaluated by the 6-minute walk distance, was improved only in the ghrelin treatment group. A mild feeling of being warm was the most frequent adverse event in this study. No treatment-related serious events were reported for either group [6].

Chronic respiratory infection is a lower respiratory tract disease that causes progressive airflow limitation, repeated exacerbation of airway infection, and destruction of airways. Bronchiectasis, cystic fibrosis, and diffuse pan bronchiolitis (DPB) often cause serious chronic lower respiratory tract infection. When the disease progresses to an advanced stage, repeated exacerbations of airway infection lead to colonization of the airways by drug-resistant pathogens and excess neutrophil-dominant inflammatory cells, which not only eradicate the exogenous pathogen but also injure the host lung. The excess inflammatory cells that accumulate in both bronchial and alveolar epithelial cells damage the host tissue by secreting proteases such as elastase and myeloperoxidase. The resultant damage to both the airways and alveolus induces deterioration of pulmonary function, which in turn causes chronic respiratory failure. Patients with advanced chronic respiratory infection often exhibit excess energy expenditure, dyspnea on effort, appetite, and weight loss. Because excess pulmonary inflammation causes the disease progression, attenuating the influx of neutrophils into the airways is a promising therapeutic target in such patients.

An open-label clinical trial of ghrelin administration to patients with serious chronic lower respiratory tract infection was conducted by Kodama et al. Synthetic human ghrelin (2 μg/kg, twice daily) was administered intravenously for 30 minutes twice daily for three weeks. Enrollment criteria for this study were as follows: productive cough with purulent sputum persisting for more than six months; multidrug-resistant pathogens isolated from sputum; greater than 7.5% of body weight lost over a period of more than six months; and body mass index less than 21. A three-week administration of ghrelin attenuated neutrophil influx to the lungs and decreased sputum levels of pro-inflammatory cytokines and neutrophil proteases. In addition, plasma norepinephrine levels were reduced; body weight and serum levels of rapid turnover proteins increased; and exercise tolerance, evaluated by the 6-minute walk distance, was improved. Thus, ghrelin administration ameliorated both the nutritional conditions and the airway inflammation of cachectic patients with chronic lower respiratory tract infection.

In the previous study, Li et al. reported that ghrelin suppressed expression of TNF-alpha–induced adhesion molecule on vascular endothelial cells [7], and Dixit et al. demonstrated that ghrelin suppressed TNF-alpha production in inflammatory cells [8]. In addition, Kodama et al. showed that ghrelin administration decreased the serum levels of soluble ICAM-1, an adhesion molecule expressed on vascular endothelial cells that regulates neutrophil adhesion [9].

Kojima et al. reported that the active form of ghrelin is acylated, and that acyl-ghrelin is produced in the stomach [10]. Acyl-ghrelin is inactivated by deacylation, yielding desacyl-ghrelin. Octanoic acids, which are omega-3 polyunsaturated acids, are indispensable for the acylation of ghrelin, and the octanoic acids are thought to be important for its activity. Yamato et al. reported that oral octanoic acids significantly increased plasma levels of ghrelin and food intake in an animal model [11]. On the other hand, it was unknown whether increased intake of the octanoic acids made plasma levels of acyl-ghrelin higher in humans. Ashitani et al. conducted an open-label clinical trial based on the hypothesis that increased intake of octanoic acids would upregulate acyl-ghrelin synthesis. The target patients of this study were cachectic patients with chronic respiratory failure.
The study population included patients with bronchiectasis, COPD, and pulmonary tuberculosis sequelae. An octanoic acid–rich formula was administered orally to enrolled patients for two weeks. Plasma levels of acyl-ghrelin were increased significantly in comparison with controls five hours after a single oral administration of octanoic acid–rich formula. By contrast, plasma levels of desacyl-ghrelin were unchanged after administration of the formula. After a two-week administration of octanoic acid–rich formula, BMI, appetite score, and the levels of rapid-turnover proteins such as prealbumin, transferrin, and retinol-binding protein were increased in a statistically significant manner. Moreover, plasma levels of rapid-turnover proteins were increased only in the 2 μg/kg group. No treatment-related serious events were reported for either group.

Cachexia often occurs in patients with advanced chronic respiratory disease, and is associated with a poor prognosis. Small clinical trials of ghrelin administration to cachectic patients with chronic respiratory disease resulted in improvements of nutritional status, exercise capacity, and QOL. However, these clinical studies had many limitations, and many issues must be solved before ghrelin can be applied to clinical use. Although further investigations are needed, ghrelin is expected to become a novel therapy for chronic wasting disease with cachexia.

References

1. Schols AM (2002) Pulmonary cachexia. Int J Cardiol 85: 101-110.
2. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ (1997) Wasting as independent risk factor for mortality in chronic heart failure. Lancet 349: 1050-1053.
3. Agusti AG, Sauleja J, Miralles C, Gomez C, Togores B, Sala E, Batle S, Busquets X (2002) Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166: 485-489.
4. Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF (1996) Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax 51: 819-824.
5. Wilson DO, Rogers RM, Wright EC, Anthonisen NR (1989) Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis 139: 1435-1438.
6. Miki K, Maekura R, Nagaya N, et al. (2012) Ghrelin treatment of cachectic patients with chronic obstructive pulmonary disease: a multicenter, randomized, double-blind, placebo-controlled trial. PLoS One 7: e35708.
7. Li WG, Gavril D, Liu X, Wang L, Gunnlaugsson S, Stoll LL, McCormick ML, Sigmund CD, Tang C, Weintraub NL (2004) Ghrelin inhibits proinflammatory responses and nuclear factor-kappaB activation in human endothelial cells. Circulation 109: 2221-2226.
8. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, Lillard JW, Taub DD (2004) Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest 114: 57-66.
9. Kodama T, Ashitani J, Matsumoto N, Kangawa K, Nakazato M (2008) Ghrelin treatment suppresses neutrophil-dominant inflammation in airways of patients with chronic respiratory infection. Pulm Pharmacol Ther 21: 774-779.
10. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402: 656-660.
11. Yamato M, Sakata I, Wada R, Kiyai H, Sakai T (2005) Exogenous administration of octanoic acid accelerates octanoylated ghrelin production in the proventriculus of neonatal chicks. Biochem Biophys Res Commun 333: 583-589.