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GLP-1 receptor agonist exacerbates mucus hyper secretory phenotype in βENaC-transgenic mouse with obstructive lung diseases

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Chronic obstructive pulmonary disease (COPD) is mainly characterized by airway mucus obstruction, chronic inflammation and emphysema. Identification of novel factors that control the COPD pulmonary phenotypes is an important issue for better treatment of COPD patients. Glucagon like peptide-1 (GLP-1) is a gastrointestinal hormone and because of its pancreatic supporting function, GLP-1 receptor agonist is clinically used as a drug for the treatment of type-2 diabetes. Interestingly, GLP-1 receptor is highly expressed in lung tissue compared with other tissues. But little is known about the physiological and pathophysiological roles of GLP-1 in lung. Here, we showed that intratracheal treatment of airway specific βENaC (epithelial Na+ channel β subunit)-transgenic mice, a murine model of COPD that basically exhibits airway mucus obstruction with GLP-1 receptor agonist Exendin-4 (10 pmol/day, 2 weeks) significantly up regulates mucin gene expression in lung tissue. Moreover, Exendin-4 significantly increased the alveolar mean linear intercept (MLI), a measure of emphysema in βENaC-Tg mice. Notably, GLP-1 receptor agonist (Exendin-4 and Liraglutide) treatment (0.1 nM, 6-12 hours) also enhanced mucin expression in β/γENaC-over expressing 16HBE14o-cells and the effect was possibly induced by p38 MAP kinase pathway. Despite observations of Exendin-4-dependent mucin up regulation in WT mice and parental 16HBE14o cells, exacerbation of pulmonary phenotypes was not observed in these conditions. Together, our studies demonstrate that pulmonary GLP-1 signal exacerbates the phenotypes of βENaC-Tg mice at least partly viap38MAPK-dependent mucin induction and our data may caution against the clinical use of inhaled GLP-1 receptor agonist in COPD patients with type-2 diabetes.

Biography

Hirofumi Nohara has completed his undergraduate degree from the School of Pharmacy, Kumamoto University (2010-2013), Laboratory studies at the Department of Molecular Medicine, School of Pharmacy, Kumamoto University (2012-2013) and completed Master's course from the Department of Molecular Medicine, Graduate School of Pharmaceutical Sciences, Kumamoto University (2014-2015). He is currently a Doctoral student at the Department of Molecular Medicine, Graduate School of Pharmaceutical Sciences of Kumamoto University, Japan.

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