

Induction of airway remodeling by repeated citric acid exposure in guinea-pig cough model

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BACKGROUND: Airway remodeling is a prominent feature in chronic cough. We previously studied 22days-model of citric acid induced cough model of guinea pigs. There we found that repeated cough itself induced increase of airway smooth muscle area in the peripheral airways, associated with increased number of cough. However, pathological changes of airways produced by mechanical stress with cough itself in more prolonged cough models are still unknown.

OBJECTIVE: To study pathological changes in the airways in prolonged cough models of guinea pigs.

METHODS: Guinea pigs were assigned to treatment with citric acid inhalation (CA), or citric acid inhalation with codeine pretreated (COD), or saline solution inhalation (SA). Intervention period is up to 6weeks (22 days or 43 days). All animals were challenged with 0.5 M citric acid on the first day and the last day of exposure. Terbutaline was administered in inhalation to prevent bronchoconstriction prior to citric acid induction and to SA group. Codeine was delivered to inhibit cough prior to citric acid induction in COD group. Animals were repeatedly challenged with citric acid or saline solution 3 times weekly. Number of cough was counted. 72hr after the last exposure, lung specimens were obtained for pathological analysis.

RESULTS: Number of coughs in CA group increased in both 22 days and 43 days of exposure compared with SA and COD group. Basement membrane thickness in trachea (Tra-BM) increased in CA group after 43 days of exposure compared with COD and SA group. The thickness of Tra-BM correlated with cough numbers when all 3 groups of 43 days-exposure were analyzed together. There was no remarkable difference of Tra-BM among 3 groups with 22 days of intervention. Area of airway smooth muscles (ASM index) in small airways increased in CA group after both 22 days and 43 days of exposure compared with SA group. ASM index in small airways increased significantly in CA group after 22 days exposure compared with COD group, but there was no significant difference between the two groups after 43days of exposure. ASM index in small airways correlated with cough numbers when all 3 groups of 22-days exposure or 43 days-exposure were analyzed together.

CONCLUSIONS: We confirmed that ASM index increased by citric acid exposure for 22 days and firstly showed that thickness of Tra-BM increased by prolonged exposure for 43 days. Repeated cough may lead to airway remodeling, which was associated with increased number of cough. The mechanical stress evoked in airway may contribute to a vicious cycle of cough persistence by inducing airway remodeling.