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Effects of Bronchoconstriction on the Cough Reflex in the Cat

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The present study was aimed to analyse the influence of bronchoconstriction (Carbachol, 10 μg/kg, i.v.) on the cough response to mechanical stimulation of the tracheal mucosa. Experiments were performed in anaesthetised and spontaneously breathing cats, using the isolated glottis technique. Airflow, pleural pressure, subglottic pressure, blood pressure and total lung resistance were recorded. During bronchoconstriction, the cough response was inhibited significantly as shown by the decrease in the number of cough efforts ($p<0.001$), in maximum flow during inspiratory ($p<0.001$) and expiratory ($p<0.001$) movements and in the change of the expiratory ($p<0.01$) and inspiratory ($p<0.01$) pleural pressures. The mechanical stimulation of the tracheal mucosa evoked always a prolonged decrease of the larynx resistance, including those cases with inhibition of the cough. This study shows that the activation of some type of receptors during bronchoconstriction can modify the cough response to mechanical stimulation of the tracheal mucosa. On the other hand, the widening of the glottis, an associated component of the cough response, can be obtained separately, suggesting that the laryngeal response is centrally integrated via different mechanisms.

Key words: Cough, Bronchoconstriction, Laryngeal resistance.

Previous reports have characterised different aspects of the respiratory reflexes of the upper airways (7, 11, 13, 15, 20-25, 28-30, 32–35). The function of the larynx is important in these reflexes since changes in its diameter can modify greatly the total airway resistance (7, 12-14, 22, 23, 29, 31, 34, 35). During eupnea, movements of the vocal cords have been described to appear in synchrony with the respiratory cycle, including an increase in larynx resistance

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during expiration (2, 10, 11, 17, 31). In dog and cat, the study of the cough reflex has shown a significant decrease in laryngeal resistance during the rapid respiratory movements that characterise the cough burst (4, 5, 11, 13, 15, 20-24, 30). In agreement with previous results, the study of the discharge pattern of laryngeal motoneurons, located in the nucleus ambiguus, has shown a tonic activity of the inspiratory laryngeal motoneurons during the cough (4, 5). These data have modified the classic description of the cough reflex response as convulsive contractions of expiratory muscles preceded by a glottic closure (29, 35).

In previous studies, the pharmacologically-induced bronchoconstriction was shown to be accompanied systematically by an increase in larynx resistance (6, 12) while bronchodilation was by a decrease of the larynx resistance (12, 14, 16). Recent experiments on the activity of laryngeal motoneurons during bronchoconstriction suggest the existence of a bronchial reflex mechanism which determines a glottic constriction, coinciding with an increase in the activity of inspiratory and expiratory laryngeal motoneurons (5).

The present study was aimed to analyze the influence of the bronchomotor tone in the cough response elicited by mechanical stimulation of the tracheal mucosa in cat. Taking into account the described correlation between lung and larynx resistances (6, 11, 12, 14), it seemed interesting to study the changes of the larynx resistance during the cough reflex in bronchoconstriction.

Materials and Methods

Experiments were performed on 21 adult cats (3.23 ± 0.37 kg). Animals were anaesthetized with a mixture of Ketamine and Xylacine (15 mg/kg and 1 mg/kg, i.m.). Supplemental doses were administered when necessary.

A double «T» cannula, composed of two independent branches, was inserted in the trachea using the in situ isolated glottis technique (20, 23, 33) with some modifications (6, 12). Airflow was measured from a Fleisch pneumotachograph head attached to the caudal part of the cannula. Subglottic pressure was determined by passing a constant stream of humidified warm air (37 °C, 1 l/min) through the rostral part of the cannula. In these conditions, subglottic pressure was considered as a valid index for laryngeal resistance. Femoral artery and vein were cannulated and an air-filled polyethylene catheter was inserted in the pleural space. Airflow, pleural pressure, subglottic pressure, arterial pressure and electrocardiogram were recorded. Total lung resistance was calculated from the transpulmonary pressure/respiratory airflow relation (X, Y) and displayed on a digital oscilloscope. Transpulmonary pressure was obtained using a differential pressure transducer attached to the pleural and tracheal cannula.

These parameters were obtained before and during tracheal stimulation in both control and bronchoconstriction conditions. The bronchoconstriction was induced by a single dose of Carbachol (carbamilcholine chloride, 10 μg/kg, i.v.). The mechanical stimulation was made systematically (with a nylon fibre introduced trough the cannula) in the posterior wall of the medial portion of the extrathoracic tracheal mucosa.

The cough response was analysed by measuring the number of cough efforts, the inspiratory and expiratory maxima flows, the inspiratory and expiratory pleural pressures, the subglottic pressure and the subglottic pressure index (the ratio between the values of subglottic pressure before eliciting the reflex —in control or bronchoconstriction— and that obtained during the reflex).

The statistical analysis was performed by using the Student's *t* test and one way analysis of variance tests.

Tabla I. *Respiratory changes during the cough*
The statistical significances are referred to the variations of the cough during bronchoconstriction related to the cough during control. Number of animals per group, 21.

	Control (n = 21)		Bronchoconstriction (n = 21)	
	before cough	during cough	before cough	during cough
Number of cough efforts	—	5.57 ± 0.97	—	1.02 ± 0.81***
Inspiratory maximum flow (ml/s)	9.32 ± 1.33	28.71 ± 3.77	7.42 ± 1.35	17.28 ± 10.22***
Expiratory maximum flow (ml/s)	8.41 ± 1.15	43.28 ± 2.06	6.52 ± 1.16	23.71 ± 15.44***
Inspiratory pleural pressure (cm H_2O)	−2.19 ± 0.26	−5.61 ± 0.65	−6.38 ± 0.71	−6.55 ± 0.50***
Expiratory pleural pressure (cm H_2O)	−0.49 ± 0.11	+6.96 ± 0.19	+0.87 ± 0.36	+3.69 ± 2.56**
Subglottic pressure (cm H_2O)	1.25 ± 0.19	0.88 ± 0.22	2.14 ± 0.21	1.43 ± 0,19
Subglottic pressure index	0.69 ± 0.15		0.65 ± 0.17	

*** $p < 0.001$; ** $p < 0.01$

Results

The cough reflex induced by the mechanical stimulation of the tracheal mucosa in control situation consisted of a variable number of cough efforts defined by the presence of an increase in inspiratory and expiratory flows ($p<0.001$ in both cases), an increase in inspiratory and expiratory pleural pressures ($p<0.001$ in both cases) and a decrease in the subglottic pressure ($p<0.01$), suggesting a maintained decrease in the resistance of the larynx to airflow (fig. 1 and table I: control, before cough and during cough).

During the pharmacological bronchoconstriction, the total lung resistance increased from 10.23 ± 3.31 to 56.41 ± 9.79 cm H_2O/l/s ($p<0.001$). As compared to the one during controls, the cough reflex response obtained during bronchoconstriction was characterised by: an abolition of the response in 30 % of the animals; a decrease in the number of cough efforts; a decrease of inspiratory and expiratory maxima flows; a decrease in the amplitude of the changes in expiratory and inspiratory pleural pressures; and, finally, a sus-

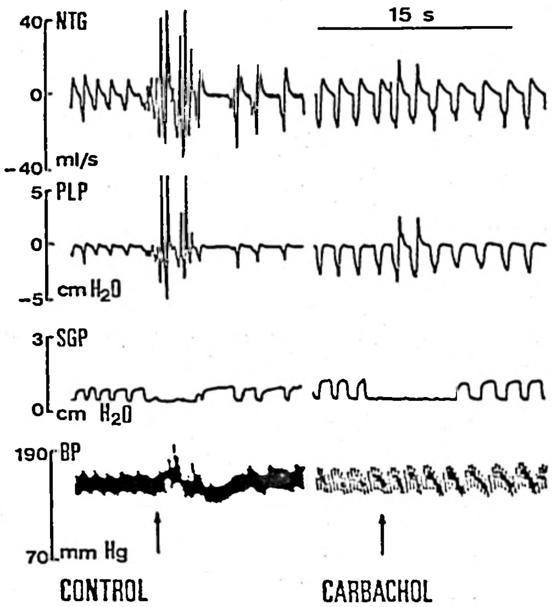

Fig. 1. *Cough response elicited by mechanical stimulation of the tracheal mucosa in both control and bronchoconstriction conditions.*
During bronchoconstriction, there is an inhibition of the cough response while the glottic dilation is maintained. The arrows indicate the onset of the stimulation. From top to bottom: pneumotachogram (NTG), pleural pressure (PLP), subglottic pressure (SGP) and blood pressure (BP).

tained decrease in subglottic pressure, even in those cases with abolition of the cough. The subglottic pressure index was similar in both control and during bronchoconstriction (table I, fig. 1).

Discussion

The results of the present study show that the bronchoconstriction provoked by carbachol, diminishes considerably, or even abolishes, the cough response elicited by the mechanical stimulation of the tracheal mucosa. However, this stimulation always evoked a maintained decrease in larynx resistance, including those cases with cough inhibition.

Different types of airway receptors mediate cough and reflex bronchoconstriction (1, 3, 7, 8, 18, 23-27, 34, 35). Their distribution is not uniform along the respiratory tract (2, 3, 8, 18, 25, 26, 29, 31, 35). The intrapulmonary airways seem to be more sensitive to mediators and some irritants. C-fibres appear to be predominant in that region (9, 18, 26, 27, 35). Larynx and carina are particularly sensitive to mechanical and to chemical stimuli. The highest density of rapidly adapting receptors has been described in this region of the upper airways (1-3, 11, 20-25, 29, 31, 32, 35).

Most of the recent reports about cough response have stimulated C-fibres selectively with capsaicin and tartaric acid (9, 18, 25-27). These drugs induce cough and a transient increase in airways resistance. Bronchoconstriction has been suggested to be a reflex component always present in the cough response, in order to increase air linear velocities in the lower respiratory tract (11, 13, 16, 22, 23, 27, 34, 35). Nevertheless, cough and bronchoconstriction can be separated in different circumstances (1, 7, 8, 25-27) although they have been defined as components of the same reflex response.

There is less information concerning the respiratory reflexes elicited by mechanical stimulation of the upper airways, although they mediate an important type of cough response (11, 13, 15, 20-24, 29, 36). The detailed study of the described respiratory parameters has allowed to characterise the modifications of the cough response in bronchoconstriction. As mentioned earlier, cough inhibition consisted of a significant decrease in the number of cough efforts, inspiratory and expiratory maxima flows and inspiratory and expiratory pleural pressures, including the abolition of the reflex response in 30 % of the animals. It is difficult to establish the types of airway receptors that participate in cough inhibition. Receptors activated during bronchoconstriction could be involved modifyng the normal response to mechanical stimulation of the tracheal mucosa. In dogs, the activation of a different type of receptors inhibited also the cough response when increasing tracheal resistance at the end of the inspiration (23).

Previous studies showed that during bronchoconstriction the increase of total lung resistance is accompanied by a narrowing effect on the diameter of the larynx (6, 14, 15). The bronchial constriction correlated with a component of glottic constriction in all cases. The cholinergic activation of the bronchomotor tone might evoke a reflex glottic narrowing which is antagonic to the glottic widening observed during cough. However, the response to the mechanical stimulation of the trachea as mentioned above, was a maintained pattern of glottic dilation during both the inspiratory and the expiratory efforts which define the cough. This response supposes a modification of the syncronic variations of the larynx resistance with the respiratory cycle observed in eupnea (2, 10, 11, 17, 31).

The apneic reflex evoked by mechanical or chemical stimulation of the laryngeal mucosa has been described in several studies (2, 3, 7, 11, 15, 22, 29, 35). The mechanical activation of receptors located in the supraglottic laryngeal mucosa determined a typical response composed of a respiratory apnea, an increase of subglottic pressure and a glottic closure (11, 15, 22, 23). In unpublished results of this laboratory, bronchoconstriction provoked also a significant decrease of the apnea duration although the increase in subglottic pressure was always present.

In conclusion, significant changes in cough and other respiratory reflex responses of the upper airways are observed in the presence of pharmacologically-induced bronchoconstriction. These results suggest that there are reciprocal influences between upper airway respiratory reflexes and the bronchomotor tone. On the other hand, the maintained decrease in larynx resistance, systematically observed as a component of the cough response, can be evoked separately. It appears that the laryngeal component of some respiratory reflexes can be centrally integrated via different mechanisms.

Resumen

Se estudia la influencia de la broncoconstricción producida por carbacol (10 µg/kg, i.v.) en el reflejo tusígeno. La tos se produce por estimulación mecánica de la mucosa traqueal, en gatos anestesiados con respiración espontánea. Se emplea la técnica de glotis aislada *in situ* y se determinan varios parámetros. Durante la broncoconstricción se produce una inhibición del reflejo caracterizada por la disminución del número de golpes de tos ($p<0{,}001$), de los flujos máximos inspiratorio ($p<0{,}001$) y espiratorio ($p<0{,}001$) y de los cambios de presiones pleurales inspiratoria ($p<0{,}01$) y espiratoria ($p<0{,}01$). La estimulación mecánica de la mucosa traqueal produce una disminución prolongada de la resistencia laríngea en todos los casos, incluso en los que se produce inhibición de la tos. Los resultados muestran que la activación de cierto tipo de receptores durante la broncoconstricción farmacológica, puede modificar el reflejo tusígeno provocado por estimulación mecánica de la mucosa traqueal. Por otra parte, la dilatación de la glotis, componente asociado a la tos, puede producirse separadamente, sugiriendo que la respuesta laríngea se integra a nivel central a través de mecanismos diferentes.

Palabras clave: Tos, Broncoconstricción, Resistencia laríngea.

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