INHIBITION OF THE VAGAL REFLEX-INDUCED TRACHEAL CONSTRICTION BY PSYCHOTROPIC DRUGS

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We investigated the effects of psychotropic drugs on reflex tracheal constriction in anesthetized, paralyzed, and artificially ventilated mongrel dogs. The tracheal constriction induced by the electrical stimulation of the central cut end of the right vagus nerve was abolished by sectioning both the left superior laryngeal and recurrent laryngeal nerves, and was reduced by a low dose of pentobarbital (3 mg/kg, i.v.). This indicates that the tracheal constriction is mediated by a vagal reflex. Chlorpromazine (3 mg/kg, i.v.) and imipramine (1-3 mg/kg) reduced the reflex tracheal constriction. Chlorpromazine and imipramine had no effect on the tracheal constriction induced by the efferent electrical stimulation of the recurrent laryngeal nerve. This suggests that the higher centers may affect the reflex airway constriction and that the present preparation may be useful for investigating the effect of psychotropic drugs on the reflex airway constriction during asthmatic attacks.

KEYWORDS—reflex tracheal constriction; afferent vagal electrical stimulation; psychotropic drug; vagus nerve

INTRODUCTION

The existence of the reflex airway constriction in asthmatic attacks has been recognized as an established fact.¹⁻³⁾ However, few studies have investigated the central autonomic neuropharmacological control of the reflex airway responses. Recently, it has been shown that the ventral surface of the medulla can play an important role in reflex airway smooth muscle responses.^{4,5)} Although it is known that emotion can exaggerate or precipitate asthma, the psychological mechanisms are unfortunately difficult to examine. It is widely believed that in asthma the emotional part of the airways is mediated by an increased parasympathetic activity.

Impulses from the airway sensory receptors can modulate the reflex airway responses. Therefore, when investigate the central effect of psychotropic drugs on reflex airway constriction, we need to exclude the participation of the airway sensory receptors in the vagal reflex arc. In the present study, we attempted to induce the reflex tracheal constriction without stimulating airway sensory

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receptors and investigated the effect of psychotropic drugs on the reflex airway constriction.

MATERIALS AND METHODS

Male mongrel dogs weighing between 10 and 13 kg were used. Experiments were carried out using the preparation for evaluating the reflex airway responses described previously.⁶⁾ Briefly, light anesthesia was induced by the intramuscular injection of ketamine hydrochloride (20 mg/kg). The cervical trachea was transected, and a tracheal cannula was inserted into the caudal side of the transected trachea. The animals were immobilized with decamethonium bromide (initial dose of 0.4 mg/kg, i.v., and supplemental doses of 0.2 mg/kg, i.v., every hour) and ventilated with room air by an artificial respirator (Shinano, SN-480-4). End-tidal CO₂ and O₂ concentrations were continuously monitored by an expired gas monitor (San-Ei, 1H21), and were maintained at an optimal ventilation level under resting conditions.

Responses of the tracheal musculature were measured as changes in the intratracheal pressure of an air-filled balloon introduced into the rostral side of the transected trachea. Recordings were made on a polygraph (Nihon Kohden, RM-6000). To induce a reflex tracheal constriction, the afferent central cut end of the afferent right vagus nerve was electrically stimulated. The stimulus was a square-wave pulse with frequency of 20 Hz; pulse duration, 1 ms; voltage, 2-10 V; applied for 10-30 s. The right superior laryngeal nerve was cut to avoid a direct effect on the tracheal smooth muscle during the vagal stimulation.

In a few experiments, the peripheral cut end of the right recurrent laryngeal nerve was electrically stimulated with a square-wave pulse: frequency, 20 Hz; pulse duration, 1 ms; voltage, 2 V; and duration, 30 s.

The drugs used were sodium pentobarbital (Tokyo Kasei), chlorpromazine hydrochloride (Contomin, Yoshitomi) and imipramine hydrochloride (Tofranil, Fujisawa). All doses are expressed in terms of the base. All drugs were administered by intravenous injection into the cephalic vein.

The results shown in the figures are expressed as mean values $\pm$ S.E. Statistical analyses were performed using the paired Student's *t* test.

RESULTS AND DISCUSSION

The tracheal constriction induced by afferent vagal stimulation was decreased to about 50% by section of the left superior laryngeal nerve or the left recurrent laryngeal nerve. The combined section of both nerves completely abolished the tracheal constriction (Fig.1; A). This indicated that the tracheal constriction is related in a vagal arc.

Pentobarbital (3 mg/kg, i.v.) reduced the tracheal constriction induced by the vagal stimulation (Fig.1; B), but had no effect on the tracheal constriction induced by the electrical stimulation of the recurrent laryngeal nerve. It has been reported that the low dose of pentobarbital inhibited neuronal discharges of the respiratory center without cardiovascular effects.⁷⁾ We demonstrated previously that the vagal reflex-induced tracheal constriction induced by histamine inhalation was reduced by the low dose of pentobarbital.⁶⁾ So it appears that the tracheal constriction induced by the vagal stimulation in this

study is mediated by a vagal reflex.

Fig.1. Effects of Section of the Left Superior Laryngeal Nerve (L.S.L.N.) and the Left Recurrent Laryngeal Nerve (L.R.N.) (A) and Pentobarbital (B) on the Tracheal Constriction Induced by Afferent Vagal Electrical Stimulation

The tracheal response was measured as changes in the intratracheal pressure (I.P.) of an air-filled balloon introduced into the rostral side of the transected trachea. Each point is the mean value with S.E. for five experiments. The changes are significant at * $p < 0.05$ and ** $p < 0.01$ against saline control values.

A dose of 1 mg/kg of chlorpromazine had no effect, but 3 mg/kg of chlorpromazine significantly reduced the reflex tracheal constriction (Fig.2). The reflex tracheal constriction was reduced dose-dependently by the i.v. injection of imipramine (1 and 3 mg/kg) (Fig.2). The tracheal constriction induced by the stimulation of the recurrent laryngeal nerve was unaffected by chlorpromazine or imipramine at the doses used.

Fig.2. Effects of Chlorpromazine and Imipramine on the Reflex Tracheal Constriction Induced by Afferent Vagal Electrical Stimulation

Each point is the mean value with S.E. for four or five experiments. The changes are significant at * $p < 0.05$ and ** $p < 0.01$ against saline control values.

It has been reported that psychotropic drugs can inhibit asthmatic attacks.^{8,9)} However, the effects of psychotropic drugs on the reflex airway constriction have not been investigated in experimental animals. In a previous study,¹⁰⁾ we reported that psychotropic drugs may inhibit the neuronal mechanisms of the brain stem, which plays an important role in the cough reflex by acting upon the feedback loop between the respiratory center and the higher centers. Although it is known that chlorpromazine exerts a relatively selective action in the reticular

activating system, the limbic system, the hypothalamus and the thalamus,¹¹⁾ the site of the inhibitory action of chlorpromazine and imipramine on the reflex tracheal constriction is not clear in this study.

Many psychotropic drugs have a peripheral effect. In the present study, chlorpromazine and imipramine had no effect on the tracheal constriction induced by the stimulation of the recurrent laryngeal nerve. This indicates that the inhibition of chlorpromazine and imipramine in this study may not be due to peripheral effects. These results suggest that the higher centers may affect the reflex airway constriction, and that the present preparation may be useful for investigating the effect of psychotropic drugs on the reflex airway constriction during asthmatic attacks.

ACKNOWLEDGMENT This work was supported in part by an Ohtani Research Grant.

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(Received June 2, 1989)