Peripheral Effects of Morphine and Codeine on the Cough Reflex

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Abstract—Peripheral effects of morphine and codeine on the cough reflex were investigated using our in situ upper trachea perfusion preparation which allows for a direct drug administration to the local site around the tracheal mucosa, this site being electrically stimulated to induce coughing. An i.a. administration of procaine or lidocaine into the tracheal vascular bed inhibited both cough response and tracheal constriction accompanied by coughings. On the other hand, benzonatate inhibited the tracheal constriction without influencing the cough response. These results indicate that the in situ upper trachea perfusion preparation is useful for evaluating effects of drugs on the cough receptor level. Morphine, 0.1 mg, and codeine, 1.0 mg, injected intraarterially into the tracheal artery, produced no tracheal constriction. Such administrations had no influence on the cough response elicited by mucosal stimulation, whereas the tracheal constriction accompanied by cough reflex was inhibited by both drugs. On the other hand, both drugs inhibited the bronchoconstriction induced by electrical stimulation of the vagus nerve. These findings suggest that both morphine and codeine inhibit the tracheal constriction accompanied by cough reflex without producing a tracheal constriction, in addition to their central antitussive action.

The antitussive effect of morphine and codeine is based on actions on central nervous system (1, 2). On the other hand, these agents may also reportedly produce airway constriction due to their peripheral actions (1, 3–6). Since airway muscular tonus is significantly involved in cough mechanisms (6–8), there is the possibility that morphine and codeine may peripherally influence cough reflex. The peripheral effects on the cough reflex, including their effects on the initiation stage of cough, have not hitherto been reported.

We described previously the in situ upper trachea perfusion preparation (9) in which drugs can be administered directly to the site where cough-induced stimuli are applied. In the present study, at first, we confirmed that the peripheral antitussive effects of local anesthetics can be evaluated by using this preparation, and secondly, investigated peripheral effects of morphine and codeine on the cough reflex. Effects of morphine and codeine on the bronchoconstriction induced by vagal stimulation were also investigated using the method for evaluating airway responses (10).

Materials and Methods

Mongrel dogs of either sex, weighing 10–
15 kg, were anesthetized with α-chloralose 100-150 mg/kg given i.p.

Experiments were done using the in situ upper trachea perfusion preparation (9). After an incision in the cervical midline, the left cranial thyroid artery and the muscular, pharyngeal and cricothyroid branches of the right cranial thyroid artery were all ligated. The right cranial thyroid artery was cannulated and perfused with arterial blood delivered from the right femoral artery, using a constant flow pump (Tokyo Rikakikai, C-16). Just before start of the perfusion, the animal was given heparin sodium, 500 units/kg i.v., and 100 units/kg were additionally given i.v. at hourly intervals. The systemic arterial blood pressure was monitored from the catheterized left femoral artery.

The cervical trachea was exposed, and transected at about 7 cm caudal to the larynx leaving the membranous wall intact. The membranous wall at the transected site was ligated with a thread to interrupt blood flow passage across the wall, while taking care not to disturb the recurrent laryngeal nerves. Responses of the tracheal smooth muscle were measured as changes in the intratracheal pressure (IP) of an air-filled balloon introduced into the rostral side of the transected trachea. The air-filled balloon was connected to a pressure transducer (Nihon Kohden, LPU-0.1) through polyethylene tubing. Respiratory and cough responses were measured using a pneumotachograph (Nihon Kohden, MFP-1T) via a cannula inserted into the caudal side of the transected trachea. Recordings were made on a polygraph (Nihon Kohden, RM-150).

The cough reflex was elicited with electrical stimuli to the membranous wall mucosa of the trachea perfused with the femoral blood. A silver disc electrode was used for the electrical stimulation. The electrode was placed between the air-filled balloon and the membranous wall mucosa. The parameters of electrical stimulation used in inducing coughs were a square-wave pulse with a 20 Hz frequency, the duration of pulse 1.0 msec, the voltage 8-10 V and the duration of application 10 sec. Evaluation of the cough response was made by changes in frequency of coughs.

A part of experiment was done using the in situ right bronchial artery perfusion preparation (10). The animals were immobilized with decamethonium bromide (initial dose 0.4 mg/kg i.v. and supplemental doses 0.2 mg/kg i.v. every hour), and ventilated artificially through a tracheal cannula connected to a positive respiratory pump (Natsume, KN-50) at a constant volume and a frequency of 20 breaths/min. The chest was opened at the right fourth intercostal space. After heparinization (initial dose 500 units/kg i.v. and supplemental doses 100 units/kg i.v. every hour), the right bronchial artery was cannulated and perfused with arterial blood delivered from the right femoral artery, using a constant flow pump. The right vagus nerve in the neck was identified and cut. The peripheral end of vagus nerve was electrically stimulated with square-wave pulse of a 20 Hz frequency, the duration of pulse 1.0 msec, the voltage 4-6 V and the duration of application 10 sec. The bronchoconstrictive responses induced by electrical stimulation of the vagus nerve were measured by a modification of the Konzett-Rössler method (11). The ventilation overflow was measured with a differential flowmeter (Nihon Kohden, RFJ-5) as an index of the change in airway resistance.

Drugs used in this study were morphine hydrochloride (Takeda), codeine phosphate (Sankyo), procaine hydrochloride (Sanko), lidocaine hydrochloride (Teikoku Kagaku) and benzonatate (Tessalon®, CIBA). Doses of all drugs used refer to their bases. All
drugs were dissolved in saline solution. Drug solutions were closely injected in a volume of 0.05 ml in 20 sec or infused with a pump for 5 min at a rate of 0.17 ml/min into the rubber tubing just proximal to the perfused artery.

RESULTS

An application of 10 sec of electrical stimuli on the tracheal mucosa perfused with femoral blood induced 5-9 coughs which were accompanied by an increase in IP and a slight decrease in systemic blood pressure.

A close i.a. infusion or injection of saline affected neither the cough response nor the change in IP and systemic blood pressure elicited by electrical stimulation on the mucosa.

A close i.a. infusion of procaine (0.85 mg/min) for 5 min inhibited both the tracheal constriction and cough response elicited by the mucosal stimulation. The inhibition disappeared about 30 min after cessation of the infusion (Fig. 1).

A close i.a. infusion of lidocaine (0.85 mg/min) inhibited slightly the cough response as well as the increase in IP. An infusion of lidocaine at 1.7 mg/min effectively inhibited the both responses for at least 5 min after cessation of the infusion (Fig. 1).

A close i.a. infusion of benzonatate (0.85 mg/min) markedly reduced the increase in IP by the mucosal stimulation with no influence on the cough response. The inhibition disappeared about 30 min after cessation of the infusion (Fig. 2).

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Fig. 1. Effects of procaine and lidocaine on the cough response (■ ■ ■) and the increase in intratracheal pressure (△ △ △) elicited by electrical stimulation of the tracheal mucosa. Procaine and lidocaine were infused close i.a. in a dose of 0.85 and 1.7 mg/min, respectively, for 5 min. The stimuli were given at 1, 3 and 5 min after start of and 3, 5, 10, 15 and 30 min after cessation of a close i.a. infusion. The ordinate gives percentage of control response. Each column is the mean with S.E. for five experiments.
A close i.a. administration of morphine (0.1 mg) had no direct effect on IP. The increase in IP elicited by the mucosal stimulation was markedly inhibited for at least 15 min, although the concomitant cough response evoked by the stimuli was unaltered (Fig. 3).

A close i.a. injection of codeine (1.0 mg)
also had no direct effect on IP. As seen with morphine, the tracheal constriction induced by electrical stimulation was effectively inhibited by codeine with no influence to the cough response (Fig. 4).

An i.v. administration of morphine (0.1 mg/kg) and codeine (1.0 mg/kg) inhibited both the cough response and tracheal constriction induced by the mucosal stimulation for at least 15 min (Fig. 5).

Marked bronchoconstriction was observed by electrical stimulation on the peripheral end of vagus nerve. A close i.a. injection of saline had no effect on the bronchoconstriction induced by the electrical stimulation of vagus nerve. A close i.a. injection of morphine (0.1 mg) and codeine (1.0 mg) had no direct effect on airway resistance. Both drugs inhibited the bronchoconstriction induced by the vagal stimulation (Fig. 6).

**DISCUSSION**

It is considered that drugs which can anesthetize cough receptors may peripherally block or alleviate coughs. Widdicombe found that inhaled procaine had an antitussive effect in the cat (6). Kasé reported that procaine injected into the femoral vein or
cisterna cerebellomedullaris produced antitussive effects in the dog (12). An intravenous administration of procaine (13) or lidocaine (14) also produced antitussive effect clinically. In our experiment, an i.a. administration of procaine and lidocaine inhibited coughs peripherally.

The antitussive effect of benzonatate is now ascribed to its highly selective local anesthetic action on pulmonary stretch receptors (15, 16). The anesthetic activity of benzonatate to the stretch receptors is 25 times as potent as that of procaine and 10 times as potent as lidocaine (16). Furthermore, benzonatate was more potent than procaine and lidocaine in conduction, infiltration and surface anesthetic activities (16). However, benzonatate, unlike procaine and lidocaine, had no effect on the cough response when given close i.a. to the stimulated site for inducing coughs. Yuizono (17) found that an i.v. administration of benzonatate had no anesthetic effect on the sensory nerve endings in the dog trachea. It is difficult to account for these findings as a result of local anesthetic action. On the other hand, we demonstrated that benzonatate, which was administered directly into the peripheral airway other than the stimulated site for inducing coughs in the upper trachea, reduced the frequency of cough reflex (8). Therefore, there seems to be a difference between the action on the pulmonary stretch receptors and that on the tracheal cough receptors.

The above results indicate that the in situ upper trachea perfusion preparation is useful for evaluating effects of drugs on the cough receptor level.

The doses of morphine (0.1 mg i.a.) and codeine (1.0 mg i.a.) used in this study were chosen in the light of their 50% antitussive doses (0.1 and 1.0 mg/kg i.v., respectively) (18) in conscious and unrestrained animals. Morphine, 0.1 mg/kg i.v., and codeine, 1.0 mg/kg i.v. produced cough-suppressing effects as did in conscious and unrestrained animals. Therefore, taking the blood volume of the tracheal segment perfused into consideration, the i.a. administration doses we gave are considered to bring about sufficiently higher concentrations in the tracheal vascular bed than those attained by intravenous administrations of the antitussive doses.

In our study, neither the i.a. doses nor i.v. antitussive doses of morphine and codeine...
constricted the tracheal muscle. Our finding is coincident with the view (1) that codeine in a usual clinical therapeutic dose range does not produce airway constriction. On the contrary, both drugs rather markedly inhibited the tracheal muscular constriction accompanied by cough reflex. On the other hand, both drugs inhibited the bronchoconstriction induced by electrical stimulation of the vagus nerve. This result suggests that morphine and codeine inhibit the release of acetylcholine from the vagus nerve endings. Both Schaumann (19) and Paton (20) have shown that morphine inhibits the release of acetylcholine from the isolated guinea-pig ileum suspended in eserined physiological salt solution. The output of acetylcholine from the perfused anterior horn of a lateral ventricle of cat was reduced by morphine injection (21). Kennedy and West (22) suggested that morphine produces a relatively specific inhibition of the release of acetylcholine from cardiac postganglionic cholinergic fibers. In a previous paper (9), we strongly suggested that the tracheal constriction observed during coughs may be attributed to a vagal activity via central nervous system. Therefore, the inhibitory actions of morphine and codeine on the tracheal constriction might be due to a reduction in the amount of acetylcholine released from endings of descending vagal nerves in the trachea.

A local administration of morphine or codeine at the site on which electrical stimuli for inducing coughing were given had no effect on the cough response itself. But, both drugs inhibited the tracheal muscular constriction accompanied by cough reflex. These findings suggest that both morphine and codeine in addition to their central antitussive action, inhibit the tracheal constriction accompanied by cough reflex without producing a tracheal constriction.

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