Effects of Methysergide on the Cough Reflex

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Abstract—The present study had two basic purposes: 1) to observe the effect of methysergide on the cough reflex and 2) to investigate the effect of methysergide on the antitussive effect of dextromethorphan. Male and female cats were anesthetized with pentobarbital-Na. Respiration and cough reflex were measured using a pneumotachograph via a cannula inserted into the trachea. The cough reflex was elicited by electrical stimuli to the superior laryngeal nerve. Methysergide (3 mg) injected into the vertebral artery increased the number of coughs and respiratory frequency. Dextromethorphan in a dose of 3 mg inhibited the cough reflex. Methysergide (1 and 3 mg) reduced the antitussive effect of dextromethorphan in a dose-dependent manner, but did not inhibit the excitatory effect on respiratory frequency. These findings might indicate that the central serotonergic system has an inhibitory role on the cough reflex and may be related to the antitussive mechanisms of dextromethorphan.

Some recent studies have provided evidence indicating that monoaminergic neuronal pathways may be involved in respiratory control (1-3). Both histochemical (4) and biochemical (5) studies have demonstrated that serotonergic neurons are located near or within the brain stem areas associated with respiratory function. Furthermore, Flórez et al. (1) and Armijo and Flórez (6) concluded that an increase in serotonin levels in the brain stem had a depressant influence upon the respiration. Kamei et al. (7) demonstrated that the increase of brain serotonin level in the cats caused the depression of cough reflex. Thus, it is considered that serotonin neurons may have important interactions with the central neuronal mechanisms in the cough reflex. Moreover, it is expected that serotonergic mechanisms may be involved in the central mechanisms in the cough depressant effect of antitussive drugs. In order to investigate the functional organization of the central neuronal mechanisms in the cough reflex, we attempted to examine the effect of methysergide, a serotonin receptor blocker, on the cough reflex. Thus, the present study had two basic purposes: 1) to observe the effect of methysergide on the cough reflex and 2) to investigate the effect of methysergide on the antitussive effect of dextromethorphan.

Male and female cats (weight range between 2.0-3.5 kg) were anesthetized with sodium pentobarbital, 30 mg/kg, given i.p. After an incision in the cervical midline, the cervical trachea was cannulated. Respiration and cough reflex were measured using a pneumotachograph via a cannula inserted into the trachea. The cough reflex was elicited by electrical stimuli to the central cut end of the superior laryngeal nerve (8). The parameters of electrical stimulation were a square-wave pulse with a 20 Hz frequency, pulse duration of 1 msec, voltage of 0.6-1.2 V and a 10 sec duration of application. The stimuli were given at 1, 3, 5, 10, 15 and 30 min after drug injection. Methysergide was injected 5 min before dextromethorphan injection. The drugs used in this study were methysergide hydrogenmalate (Sandoz) and...
dextromethorphan hydrobromide (Shionogi). All doses were expressed in terms of the base. All drugs were dissolved in saline solution and injected close i.a. into the vertebral artery.

Figure 1 shows the effect of methysergide on the respiration and cough number. The electrical stimuli to the superior laryngeal nerve induced stable and reproducible coughs (6.0±0.8 coughs/stimulation). Methysergide in a dose of 1 mg had no effect on the cough number. However, 3 mg of methysergide increased the cough number. A significant increase of cough number was observed 5 min after the methysergide (3 mg) injection, and the increase in the cough number was about 30% against the control value. During the control period, the respiratory frequency was 30.0±1.0 breaths/min. No change in respiratory frequency was found following the 1 mg of methysergide injection. On the other hand, 3 mg of methysergide increased the respiratory frequency as it did the cough number. Figure 2 shows the effect of methysergide on the antitussive effect of dextromethorphan. An i.a. administration of

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![Figure 1](image1.png)

**Fig. 1.** Effects of methysergide on the cough reflex (A) and respiratory frequency (B). Methysergide was injected i.a. in doses of 1 mg (■) and 3 mg (▲). Each column represents the mean with S.E. for four to five experiments. The change is significant at *P<0.05 against the saline control (■) value.

![Figure 2](image2.png)

**Fig. 2.** Effects of dextromethorphan and of dextromethorphan in the presence of methysergide on the cough reflex. Dextromethorphan (3 mg, △) and methysergide (1 mg, ○; 3 mg, ●) were injected i.a. Each point represents the mean with S.E. for four experiments. The change is significant at *P<0.05 and **P<0.01 against saline control (——) values.
Dextromethorphan inhibited the cough reflex. The maximum effects of dextromethorphan on the cough reflex appeared about 3 min after the dextromethorphan injection. The inhibition disappeared about 30 min after administration. Methysergide inhibited the antitussive effect of dextromethorphan in a dose-dependent manner. Although the data were not shown here, the respiratory excitatory effect of dextromethorphan was not changed by administration of methysergide (1 and 3 mg).

There are some indications in the literature (2, 3, 6, 7) that the increase in serotonin levels in the brain stem has a depressant influence on the respiratory and cough reflex. It is well-known that the opiate influences the concentration of neurotransmitters in the central nervous system. Further, Flórez et al. (1) concluded that serotonin in the brain stem is a synergistic factor with the action of morphine, and that the presence of serotonin is needed in order for morphine to be fully active on the respiratory center. Thus, it is supposed that serotonergic mechanisms closely interact with opiate receptor mechanisms. Since methysergide increased the respiratory frequency and the cough number, central serotonergic mechanisms seem to play an inhibitory role on the respiratory activity.

Methysergide is a competitive inhibitor of serotonin receptor (9) and is highly effective in antagonizing central serotonin (10, 11). In the present study, methysergide inhibited the antitussive effect of dextromethorphan by more than 60%, substantiating the contention that serotonin may be the responsible neurotransmitter in the central mechanisms of the cough reflex. A lower dose of methysergide (1 mg, i.a.) antagonized the antitussive effect of dextromethorphan without respiratory excitatory response. Furthermore, the respiratory excitatory effect of dextromethorphan was not affected by methysergide. This result indicates that the serotonergic mechanisms may not be involved in the respiratory excitatory effect of dextromethorphan. Thus, it is suggested that the central serotonergic system might be involved in an inhibitory mechanisms of the cough reflex, and the system may be related to the antitussive mechanisms of dextromethorphan.

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