Effects of Nicotine on Gastric Contractile Response to Stimulation of the Vagal Afferent Fibers in Cats

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Abstract—Effects of nicotine on the delayed gastric contraction due to vagal afferent stimulation were studied. Cats were pretreated with phentolamine (2 mg/kg, i.v.) and propranolol (1 mg/kg, i.v.). The delayed contraction was inhibited by nicotine (100 to 2000 μ g/kg, i.v.) in a dose-dependent manner. The inhibition of the delayed contraction by nicotine was blocked by hexamethonium (20 mg/kg, i.v.). The results suggested that nicotine inhibits the delayed contraction by activation of hexamethonium-sensitive inhibitory neurons in the vagal pathway to the stomach.

Recently, we reported (1, 2) that electrical stimulation of the vagal trunk in pento-barbital-gallamine anesthetized cats produced a biphasic contractile response of the stomach: an initial contraction during stimulation that may be due to stimulation of vagal efferent fibers and a delayed contraction after stimulation that may be due to stimulation of vagal afferent fibers. The initial contraction is sensitive to hexamethonium, but the delayed contraction is resistant to hexamethonium. Nicotine inhibits gastric contraction in response to stimulation of the vagus in the dog (3). However, whether nicotine acts on the vagal efferent response or the vagal afferent response is not clear. The major action of nicotine on the parasympathetic ganglion of the efferent vagus consists of an initial transient stimulation and a subsequent long lasting suppression. This study was undertaken to investigate the effects of nicotine on the hexamethonium-resistant delayed contraction of the stomach due to stimulation of vagal afferent fibers in cats.

The experimental procedures were essentially similar to those of Okamoto et al. (1, 2). Thirteen cats of either sex, weighing 2.5 to 4.0 kg, were used. The animals were deprived of food but allowed free access to water 12 hr before the experiment. Pento-

barbital sodium (60 mg/kg, i.p.) was administered. Additional amounts were administered when necessary. A tracheal cannula was inserted. The right femoral vein was catheterized, and gallamine triethiodide (20 mg/ml) was infused at a constant rate (1.48 ml/hr). Artificial respiration was maintained by a respiration pump. The respiration rate was 15/min with the air volume at 70 ml per stroke. The left femoral vein was catheterized for drug injection. The cervical vagal trunks on both sides were cut and the ends ligated. The distal trunk of the left vagus was placed on bipolar platinum electrodes and covered with cotton wool soaked in liquid paraffin. The cats were pretreated with propranolol (1 mg/kg) and phentolamine (2 mg/kg) to inhibit α - and β -adrenoceptors. Gastric motility was recorded with a balloon introduced via the esophagus. The system was filled with water and connected to a pressure transducer; thus changes in intragastric pressure were recorded. The level of intragastric pressure was set at 7 to 10 cmH₂O, and changes were recorded on a polygraph (San-ei Instrument, Tokyo, Japan) via a pressure transducer. The stimulation conditions were 10 Hz in frequency, 3 msec in duration, 15 V in intensity for 10 sec. The drugs used were nicotine and hexame-

Fig. 1. Effects of nicotine on the initial and the delayed contraction of the stomach to stimulation of the vagal trunk in cats. Vertical scale indicates 20 cmH₂O; Horizontal scale, 3 min. Stimulation of the vagal trunk (●). A: Effect of nicotine (1000 µg/kg, i.v.). B: Effect of nicotine (2000 µg/kg, i.v.). C: Effect of nicotine (2000 µg/kg, i.v.), after treatment with hexamethonium (20 mg/kg, i.v.).

thonium. The height of the contraction of the stomach before administration of drugs was regarded as 100%.

As previously reported, stimulation of the vagal trunk in cats produced both the initial contraction of the stomach during stimulation (due to stimulation of vagal efferent fibers) and the delayed contraction after stimulation (due to stimulation of vagal afferent fibers) (1, 2). In 10 cats, administration of nicotine (100 to 2000 µg/kg) produced a transient contraction of the stomach (Fig. 1, A and B). After the contraction of the stomach returned to the control level, the vagal trunk was stimulated. The pretreatment with nicotine dose-dependently inhibited both the initial and the delayed contraction (Figs. 1A, 1B and 2). The inhibitory effect of nicotine on the initial contraction lasted over 60 min, but the inhibitory effect of nicotine on the delayed contraction recovered within 5 min. In 3 cats, hexamethonium (20 mg/kg) was administered before nicotine injection. As previously reported (1), the pretreatment with

Fig. 2. Effects of nicotine on the delayed contraction of the stomach to stimulation of vagal afferent fibers in cats. Ordinate scale: % response, as compared with the control response before administration of nicotine (100 to 2000 µg/kg, i.v.). Control (○). Pretreatment with hexamethonium (20 mg/kg, i.v.) (●).

hexamethonium completely inhibited the initial contraction, but significantly augmented the delayed contraction (Fig. 1C). Pretreatment with hexamethonium inhibited the transient contraction induced by nicotine and suppressed the inhibitory effect of nicotine on the delayed contraction (Figs. 1C and 2).

We have reported that hexamethonium augmented the delayed contraction (1, 4, 5). Such augmentation is assumed to be due to blockade of the hexamethonium-sensitive inhibitory neuron. The present study demonstrated that inhibition of the delayed contraction by nicotine was abolished by treatment with hexamethonium. In autonomic ganglions, nicotine has dual actions: first, a stimulating action and then, a blocking action. Nicotine produced a contraction and then inhibited the initial contraction induced by the vagal stimulation. Both the nicotine-produced contraction and the vagal stimulation-induced initial contraction were blocked by hexamethonium. These results indicate that the inhibitory effect of nicotine on the initial contraction induced by the stimulation is due to the ganglionic blocking action of nicotine. Adrenergic inhibitory neurons on the paralytic effect of nicotine on gastric movement have been reported (3, 6, 7). In the present study, cats were pretreated with phentolamine and propranolol to inhibit α - and β -adrenoceptors. Therefore, involvement of adrenergic inhibitory neurons in the inhibitory effects of nicotine on the contraction can be ruled out. The administration of hexamethonium inhibited the initial contraction and augmented the delayed contraction, and it abolished the inhibitory effect of nicotine on the delayed contraction. Such inhibition of the delayed contraction by nicotine might be due to activation of the hexamethonium-sensitive inhibitory neurons. We have reported that naloxone enhances the delayed contraction

of the stomach by the stimulation of vagal afferent fibers, and met-enkephaline inhibits both the initial and delayed responses (2). Taken together with our previous findings (1, 2, 5), the present results suggest that in addition to classic nicotinic action on autonomic ganglion, nicotine may have nicotinic action on inhibitory enkephalinergic neurons (modulation of vagal afferent response in stomach) in the cat.

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