Involvement of Nicotinic Receptors in the Dorsal Motor Nucleus of the Vagus in Regulation of Gastric Motility in Rats

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ABSTRACT — Roles of nicotinic receptors in the dorsal motor nucleus of the vagus (DMV) in the regulation of gastric motility were investigated in urethane-anesthetized rats in which an intragastric balloon had been placed. Nicotine (0.1 nmole) microinjected into the DMV but not the nucleus ambiguous induced dual changes, a decrease followed by an increase in gastric motility. Administration of 0.1 nmole of hexamethonium into the DMV significantly inhibited the decrease in gastric motility induced by intravenously administered nicotine.

We recently reported that intracerebroventricularly (i.c.v.) administered nicotine induced dual changes, a decrease followed by an increase in gastric motility in rats (1) and that this dual effect of i.c.v.-administered nicotine was reproduced by a 10 times smaller dose of intracisternally (i.c.)-administered nicotine (2). These findings suggest that the site of action of nicotine probably resides in the lower part of the brain, such as the brain stem. In the present study, therefore, possible roles of nicotinic receptors in the dorsal motor nucleus of the vagus (DMV) in central regulation of gastric motility were investigated by administration of nicotine in rats.

Male Wistar rats weighing 350–400 g were maintained in a room at 22–24°C under a constant day-night rhythm and given food (laboratory chow, CA-1; Clea, Inc., Japan) and tap water ad libitum. Prior to each experiment, food was withheld for 24 hr but water was provided. Under anesthesia with urethane (1.2 g/kg, i.p.), a single femoral artery and vein were cannulated to monitor blood pressure and to apply test substances, respectively. Gastric motility was measured with a flaccid intragastric balloon inserted into the stomach through an incision in the fundus. After closure of the incision, 2 to 3 ml of water were introduced into the balloon to give an intragastric pressure of about 100 mmH2O. Changes in intragastric pressure induced by gastric contraction were measured using a pressure transducer connected to the balloon, and a pen writing recorder was used to monitor differences. All waves larger than 5 mmH2O in amplitude (1 mm of pen displacement vertically) were counted as contractions. The mean amplitude was calculated for consecutive 2-min periods and was taken to indicate the gastric motility.

Test substances given into the brain were dissolved in artificial cerebrospinal fluid (vehicle), the composition of which was 7.3 mg NaCl, 1.9 mg NaHCO3, 0.3 mg MgSO4, 0.2 mg CaCl2 and 0.2 mg NaH2PO4 in 1 ml of deionized water; i.e., a slight modification of the composition described by Falcon et al. (3). The solutions containing test substances were then applied into the DMV and its adjacent
area in a volume of 0.5 μl/animal through a glass micropipette (50 μm outer diameter). At the end of the experiment, the brain was removed, fixed in 10% formalin, and the frozen sections sliced at 30 μm were stained with cresyl-violet for microscopic localization of the micropipette insertion site. Student’s t-test was used for comparison between two groups, and Duncan’s multiple range test was used for multiple comparison. P values of less than 5% were considered to be statistically significant.

When the intraluminal pressure applied was about 100 mmH2O, spontaneous and rhythmic contractions of the stomach with an amplitude of 93.6 ± 8.8 mmH2O (n = 34) were observed. Because of relatively large individual variations, the results obtained were expressed as percent change of the basal value (the basal value being the mean of three values from the triplicate 2-min periods preceding administration of nicotine).

When the tip of micropipette had been placed in an area within 200 μm from the DMV, 0.1 nmole of nicotine induced dual changes, a decrease followed by an increase in gastric motility with no exceptions (n = 7) (Fig. 1). When the micropipette had been placed at a site far from the DMV, more than about 200 μm away, in 5 out of 7 instances, 0.1 nmole of nicotine did not induce any changes in gastric motility. In the other 2 instances, micropipette had passed through the DMV. Therefore, a result obtained from the experiment in which the micropipette tip had been placed in an area within 200 μm from the DMV was totalized as that by administration of nicotine into the DMV.

Nicotine (0.01 nmole) administered into the DMV produced only a decrease in gastric motility. One-half microliter of artificial cerebrospinal fluid (vehicle) given into the DMV had no significant effects on gastric motility (Fig. 1).

Administration 0.1 nmole of nicotine into the DMV elicited dual changes, a decrease followed by an increase in gastric motility. These dual changes were comparable to those by administration of nicotine intracisternally (i.c.), but the effective dose of nicotine administered into the DMV was 100 times smaller than that of nicotine administered i.c. (2). It is well-known that the cell bodies of the pre-
ganglionic neurons of the gastric vagus nerve are found in the nucleus ambiguus as well as the DMV (4). When nicotine was administered into the nucleus ambiguus, gastric motility was, however, not significantly affected. These results suggest that nicotinic receptors in the DMV but not the nucleus ambiguus are involved in the effects of centrally administered nicotine on gastric motility. In contrast to the dual changes, a decrease followed by an increase in gastric motility elicited by a higher dose of nicotine, only a decrease in gastric motility was induced by a lower dose of this alkaloid administered into the DMV. These results reveal that a larger dose of nicotine is required for inducing an increase rather than a decrease in gastric motility. The vagus nerve has two efferent components, one inhibitory and the other excitatory to the stomach. The decrease and the increase in gastric motility induced by i.c.v.-administered nicotine are mediated by the vagal inhibitory and excitatory components, respectively (1). Both central inhibitory and excitatory influences to the stomach are finally integrated in the DMV and conveyed with the vagus nerve. Therefore, different neuronal sensitivities of vagal inhibitory and excitatory mechanisms in the DMV to nicotine may explain the inability of a lower dose of nicotine to increase gastric motility.

We suggested that a smaller dose of nicotine administered intravenously (i.v.) activated nicotinic receptors in the brainstem and elicited vagally-mediated inhibition of gastric motility (2). In the present study, we examined whether or not nicotinic receptors within the DMV participated in inhibition of gastric motility induced by i.v.-administered nicotine. Nicotine at 300 nmole/kg administered i.v. decreased gastric motility, as previously reported (2). No significant changes in blood pressure were observed by i.v.-administered nicotine. In the animals in which bilateral DMV were pretreated with 0.1 nmole hexamethonium, the decrease in gastric motility induced by i.v. administered nicotine was significantly inhibited (Fig. 2). These results suggest that the DMV-mediated central inhibition of gastric motility is manifestable by intravenous administration of this alkaloid.

In the next series, the effect of nicotine mi-

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**Fig. 2.** Effect of hexamethonium on the decrease in gastric motility induced by intravenously (i.v.) administered nicotine. ○, vehicle (CSF) plus nicotine (n = 6); ●, hexamethonium, 0.1 nmole plus nicotine (n = 7). DMV, administration of hexamethonium or vehicle into the bilateral DMV. i.v., intravenous administration of nicotine, 300 nmole/kg. The results are expressed as means ± S.E. a, P < 0.01 (significantly different from the respective value just before administration of nicotine). b, P < 0.01 (significantly different from the corresponding values pretreated with vehicle alone).
croinjected into the hypothalamic regions was examined. We reported that administration 3 nmole of nicotine into the posterior part of the ventromedial nucleus of the hypothalamus significantly increased gastric acid output (5). In the present study, however, no significant changes in gastric motility was observed with 3 nmole of nicotine applied into various parts of the hypothalamus (the anterior nucleus, the paraventricular nucleus, the ventromedial nucleus, the dorsomedial nucleus, the posterior nucleus and the premamillary nucleus) (data not shown). Therefore, different from the effect of nicotine on gastric acid secretion, there is little possibility that this alkaloid administered into the hypothalamus produces any changes in gastric motility.

In conclusion, we demonstrated that nicotinic receptors in the DMV are involved in central regulation of gastric motility. However, involvement of nicotinic receptors in the solitary nucleus in nicotine-induced changes in gastric motility can not be ruled out, since the DMV and the solitary nucleus are in close proximity, and there exists a functional circuit between these two nuclei.

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REFERENCES