Central Inhibition of Gastric Motility by Intravenously Administered Nicotine in Rats

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Abstract—Effects of intravenously (i.v.) administered nicotine on gastric motility were investigated in urethane-anesthetized rats in which an intragastric balloon had been placed. I.v. administered nicotine at 75–300 nmole/kg dose-dependently decreased gastric motility. Decrease in gastric motility induced by nicotine at the dose of 300 nmole/kg was inhibited by intracisternally administered hexamethonium. Gastric motility was also decreased by intracisternally applied nicotine (1–10 nmole). These doses were much smaller than those by the intracerebroventricular route in our previous report. Bilateral vagotomy significantly suppressed basal gastric motility. In bilaterally vagotomized animals, nicotine at 1 nmole/kg but not 300 nmole/kg given i.v. significantly decreased the gastric motility maintained at a normal level by electrical stimulation of the vagus nerve. This nicotine-induced decrease in gastric motility, under conditions of electrical stimulation of the vagus nerve, was inhibited by pretreatment with phentolamine. These results suggest that a smaller dose of nicotine given i.v. activates nicotinic receptors in the brainstem and elicits vagally-mediated inhibition of gastric motility. Activation of peripheral α-adrenergic mechanisms together with that of central nicotinic mechanisms may be involved in the decreasing effects of a larger dose of nicotine on gastric motility.

Carlson et al. (1) reported inhibitory and stimulatory effects of intravenously administered nicotine on antral motility in anesthetized dogs. We have recently reported that intracerebroventricularly (i.c.v.) administered nicotine had a dual effect, a decrease followed by an increase, on rat gastric motility and that this dual effect was due to the activation of central nicotinic receptors and was mediated by the vagus nerve (2). It is well-known that peripherally administered nicotine enhances the release of catecholamines from adrenal glands and sympathetic nerve terminals. Both the catecholamines released from adrenal glands and those released via activation of the sympathetic nerve are associated with the inhibition of gastric motility (3–7). Nicotine has both stimulatory and inhibitory actions on autonomic ganglia. Moreover, nicotine micro-injected into the caudal part of the rat ventromedial hypothalamus increased gastric acid output (8). All this evidence suggested that various central and peripheral actions of nicotine might be involved in the nicotine-induced changes in gastric motility. However, there is still a paucity of information concerning the nicotine-induced changes in gastric motility. In the present study, we examined the effect of intravenously (i.v.) administered nicotine on gastric motility in anesthetized rats to elucidate how the central and peripheral nicotinic receptors are involved in the change in gastric motility induced by i.v. administered nicotine.

Materials and Methods
Male Wistar rats weighing 350–400 g were maintained at 22–24°C under a constant day-night rhythm and diet (laboratory chow, CA-1; Clea, Inc., Japan) and tap water ad libitum. Prior to each experiment, food was withheld for 24 hr, but water for drinking 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 of the fundus. After closure of the incision with purse-string sutures, 2 to 3 ml of water were introduced into the balloon to give the stomach an intraluminal pressure of about 100 mmH\(_2\)O. Changes in intragastric pressure induced by gastric contraction were measured using a pressure transducer connected to a balloon, and a pen writing recorder was used to monitor differences. All waves with an amplitude larger than 5 mmH\(_2\)O (1 mm of pen displacement vertically) were considered to be contractions. The lowest pressure in the nadirs of waves served as a measure of the tone of the gastric wall for a consecutive 30-sec period. The amplitude of contraction was taken as the difference between the peak pressure of each contraction and the tone. The mean amplitude was calculated for consecutive 2-min periods and was taken as an indication of gastric motility.

An injection needle (23 gauge) was used for the intracisternal administration of test substances. The volume for intracisternal injection was 10 \(\mu\)l/animal. Test substances given intracisternally (i.c.) were dissolved in artificial cerebrospinal fluid (vehicle), the composition of which was 7.3 mg NaCl, 1.9 mg NaHCO\(_3\), 0.3 mg MgSO\(_4\), 0.2 mg CaCl\(_2\) and 0.2 mg NaH\(_2\)PO\(_4\) in 1 ml of deionized water; i.e., a slight modification of the composition described by Falcon et al. (9). Test substances given i.v. were dissolved in physiological saline. The volume for intravenous injection was 1 ml/kg body weight.

Gastric motility was significantly suppressed in the bilaterally cervically vagotomized rats. In experiments using these cervically vagotomized animals, the distal end of the sectioned left vagus nerve was stimulated with rectangular electrical pulses, using a ring platinum electrode. As reported (2), the gastric motility elevated by electrical stimulation of the vagus nerve with 2 mA in intensity, 0.5 msec in duration and 5 Hz in frequency was comparable to the gastric motility observed in intact animals. We, therefore, used these parameters for electrical stimulation.

Student's t-test was used for comparison between two groups, and Dunncan's multiple range test was used for multiple comparison. P values of less than 5% were considered to be statistically significant.

Results

Vagally-intact animals: When the stomach was given an intraluminal pressure of about 100 mmH\(_2\)O, basal gastric motility with a frequency of 10.7±0.6 cycles per 2 min (\(n=63\)) and an amplitude of 83.6±4.2 mmH\(_2\)O (\(n=63\)) was observed.

Nicotine (75-300 nmole/kg, i.v.) dose-dependently decreased the amplitude of gastric motility (Figs. 1, 2 and 3). No significant changes in blood pressure were observed by nicotine (300 nmole/kg, i.v.).

When nicotine at 300 nmole/kg was i.v.

![Nicotine 300 nmole/kg, i.v.](image)

**Fig. 1.** A representative illustration of gastric motility in an intact rat before and after the intravenous administration of nicotine at 300 nmole/kg.
Fig. 2. Effect of intravenously (i.v.) administered nicotine on gastric motility. •, saline (vehicle) (n=5); ○, nicotine 300 nmole/kg (n=8). The results are expressed as means±S.E. *a, P<0.05 (significantly different from value just before nicotine, i.v.).

Fig. 3. Dose-response relationship between doses of nicotine administered i.v. and the decrease in gastric motility. On the ordinate, the percent change of the values of the 4-min period to those of the 0-min period; on the abscissa, doses of i.v. administered nicotine (nmole/kg). Numbers in parentheses present the number of animals used in the respective experiments.

applied 10 min after intracisternal administration of hexamethonium (10 nmole/animal), the nicotine-induced decrease in gastric motility was significantly inhibited (Fig. 4). Hexamethonium (10 nmole, i.c.) did not significantly affect the basal gastric motility.

Nicotine at 10 nmole/animal injected i.c. induced a decrease followed by an increase in gastric motility. Both changes in gastric motility elicited by nicotine were significant as compared with the control value just before administration of nicotine. When nicotine at 1 nmole/animal were i.c. injected, a significant decrease but no increase in gastric motility was observed (Fig. 5). Percent decreases in gastric motility 4 min after intracisternal administration of nicotine at 0.01, 1 and 10 nmole/animal were 11.9±24.7 (n=8), 41.7±21.6 (n=8) and 79.2±11.1 (n=5), as compared with the respective control values.

Bilaterally vagotomized animals: Bilateral vagotomy significantly suppressed basal gastric motility. In these animals, gastric motility was maintained at the normal level by electrical stimulation of the vagus nerve at 2 mA, 0.5 msec, 5 Hz. Nicotine administered at 300 nmole/kg, i.v., did not affect the gastric motility under electrical stimulation of the vagus nerve (Fig. 6).

When nicotine at 1 μmole/kg, i.v., was administered to bilaterally vagotomized rats, gastric motility, which had been maintained of the normal level by electrical stimulation of the vagus nerve, was significantly decreased (Fig. 6). This decreasing effect of nicotine on gastric motility was significantly antagonized by pretreatment with phentolamine (5 mg/kg, i.m., for 30 min) (Fig. 7). In these phentolamine-pretreated animals, pressor response to nicotine at 1 μmole/kg, i.v., was also significantly inhibited (increase in blood pressure: nicotine alone, 56.4±8.6 mmHg n=6; nicotine after phentolamine, 19.8±4.0 mmHg n=6, P<0.05).
Fig. 4. The effect of hexamethonium on the nicotine-induced changes in gastric motility. O, nicotine 300 nmole/kg, i.v. (n=8); •, nicotine, 300 nmole/kg, i.v., 10 min after hexamethonium (10 nmole, i.c.) (n=6). The results are expressed as means±S.E. a, P<0.05 (significantly different from value just before nicotine); b, P<0.05 (significantly different from corresponding value with nicotine).

Fig. 5. The effect of intracisternally (i.c.) administered nicotine on gastric motility. •, CSF (vehicle, n=6); Δ, nicotine, 1 nmole (n=8); O, nicotine, 10 nmole (n=5). a, P<0.05 (significantly different from the respective values just before nicotine).

Discussion

Intravenous administration of nicotine induced a decrease in gastric motility in rats. To test whether central or peripheral nicotinic receptors are involved in the inhibitory effect of this alkaloid on gastric motility, we examined the effect of i.v. administered nicotine on gastric motility in bilaterally vagotomized rats. In these rats, nicotine (300 nmole/kg, i.v.)-induced inhibition of gastric motility was not observed. The inhibitory effect of i.v. administered nicotine on gastric motility was, therefore, due to activation of central, but not peripheral, nicotinic receptors and was mediated by the vagus nerve, at least at the dose of 300 nmole/kg.

Intracisternal administration of hexame-
Fig. 6. The effect of i.v. administered nicotine on the gastric motility in bilaterally vagotomized rats. Gastric motility was maintained at the normal level by electrical stimulation (ES) of the vagus nerve (2 mA in intensity, 0.5 msec in duration, 5 Hz in frequency).

Fig. 7. The effect of phenolamine on the nicotine-induced decreases in gastric motility in bilaterally vagotomized rats. Gastric motility was maintained at the normal level by electrical stimulation (ES) of the vagus nerve (2 mA, 0.5 msec, 5 Hz). □, nicotine, 1 μmol/kg, i.v. (n=6); △, nicotine, 1 μmol/kg, i.v., 30 min after phenolamine (5 mg/kg, i.m.) was administered (n=6). The results are expressed as means±S.E.  a, P<0.05 (significantly different from value just before nicotine); b, P<0.05 (significantly different from the corresponding value with nicotine alone).

Thionium significantly inhibited the effect of i.v. administered nicotine, 300 nmole/kg, on gastric motility. Furthermore, i.c. administered nicotine induced a decrease in gastric motility. The dose of nicotine given i.c. was smaller than that applied i.c.v. (see later).
Therefore, it is likely that nicotine adminis-
tered i.v. stimulates nicotinic receptors in the
brain stem and then induces the vagally-
mediated decrease in gastric motility.

On the other hand, when the dose of
nicotine was increased to 1 $\mu$ mole/kg, i.v.,
gastric motility was significantly decreased
even in bilaterally vagotomized rats. It is well-
known that nicotine peripherally adminis-
tered enhances the release of catecholamines
from the adrenal glands and the sympathetic
nerve terminals, and accelerates sympathetic
nerve transmission in its smaller doses. Fur-
thermore, catecholamines inhibit gastric motility (3–5), and activation of gastric $\alpha$
-adrenergic receptor inhibits gastric acid
secretion (10, 11). Yokotani et al. (12)
demonstrated that intravenous infusion of
nicotine inhibited the increase in vagally
stimulated gastric acid output and that this
nicotine-induced inhibition of gastric acid
output was mediated by activation of gastric
$\alpha$-adrenoceptor. In the present study, de-
crease in gastric motility elicited by 1 $\mu$ mole/
kg of i.v. administered nicotine in the bilat-
erally vagotomized rats was significantly
antagonized by pretreatment with phentol-
amine, an $\alpha$-blocking agent. Elevation of
blood pressure by nicotine was also inhibited
by this pretreatment. Therefore, peripheral $\alpha$
-adrenergic mechanisms are involved in the
inhibition of gastric motility induced by a large
dose of i.v. administered nicotine.

In contrast to the effect of i.c.v. adminis-
tered nicotine, an increase following the early
decrease in gastric motility (2), no sig-
nificant increase was induced by intravenous
administration of nicotine. Then, we in-
vestigated the reason why nicotine by the
intravenous route did not induce any increase
in gastric motility. In the present study, intra-
cisternal administration of nicotine produced
a dual change in gastric motility similar to
those induced by its intracerebroventricular
administration. The effective dose of nicotine
on gastric motility by the intracisternal route,
10 nmole, was ten times smaller than that by
the i.c.v. route. It is interesting to note that
only a decrease but not an increase in gastric
motility was observed when the dose of
nicotine by the intracisternal route was
further reduced. 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
pathways one excitatory and the other
inhibitory to the stomach. Both pathways
have their cell bodies of preganglionic neu-
rons in the medulla oblongata (13). We
recently suggested that the decrease and the
increase in gastric motility induced by i.c.v.
administered nicotine is mediated with the
inhibitory and the excitatory component in
the vagus nerve, respectively (2). Therefore,
different neuronal sensitivity to nicotine
between preganglionic cell bodies of vagal
excitatory and inhibitory mechanisms may
explain the inability of i.v. administered
nicotine to increase gastric motility.

Carlson et al. (1) reported a stimulatory
effect of i.v. administered nicotine on dog
antral motility, but we did not observe any
stimulatory effect on rat gastric motility of
nicotine given by the same route. Differences
in animal species and methods used may
explain this discrepancy of our results in the
present study with theirs.

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