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Protective Effect of Nicotine on Gastrin-induced Gastric Mucosal Damage in Rats

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ABSTRACT

Conflicting data have been reported on the effect of nicotine on gastric mucosal damage. To elucidate the effect of chronic intermittent nicotine on gastric mucosal damage, intragastric nicotine (5 mg/kg, 10 mg/kg) was administered twice per day for 9 days. Gastric mucosal damage was created by s.c. injection of a large dose (1.2 mg/kg) of pentagastrin followed by pylorus ligation for 6 hours. Nicotine treated rats showed reduced gastric mucosal damage about 50% of the control. To examine the mechanism of the protective effect of nicotine, gastric perfusion experiments were done. Basal acid secretion was not affected by intragastric or intravenous nicotine. However, pentagastrin-stimulated acid secretion markedly inhibited by a bolus injection of nicotine, and this response was dose-related. These data indicates that chronic intermittent administration of nicotine protects gastric mucosa against gastrin-induced gastric mucosal damage, and nicotine-induced inhibition of gastrin-stimulated acid secretion has an important role for the protective effect of nicotine. Considering reports concerning nicotine's aggravating effect on the gastric mucosal damage, it is suggested that the methods of administration of nicotine may be an important decisive factor of the divergent action of nicotine on the gastric mucosa.

Key Words: Nicotine, Gastric mucosal damage, Gastrin, Gastric acid

INTRODUCTION

Epidemiological studies have indicated that smoking has a harmful effect on peptic ulcer disease. Smoking increased risk for peptic ulcer (Friedman *et al.*, 1974; Piper *et al.*, 1982; Kato *et al.*, 1992) and decreased healing rate (Doll *et al.*, 1958; Korman *et al.*, 1981) and increased recurrence rate (Sontag *et al.*, 1984; Korman *et al.*, 1983).

Most epidemiological studies performed by oral questionnaire and lacked scientific diagnosis. Nevertheless, duodenal ulcer seems to be related to smoking. However, studies on the effect of smoking on gastric ulcer are not clear. Studies on the effect of nicotine on gastric acidity in humans showed decreased acidity upon gastrin-stimulated state (Sonnenberg and Husmert, 1982) or no changed acidity upon basal acid secretion (Lindell *et al.*, 1992). There are also conflicting data concerning the effect of nicotine on gastric acid secretion in animals. Nicotine increased basal acid secretion in cats (Albinus *et al.*, 1988), rats (Thompson *et al.*,

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1970, 1971) and isolated parietal cell preparation(Albinus *et al.*, 1988). On the contrary, a series of papers reported that nicotine inhibited gastric acid secretion in rats (Kowalewski, 1974; Thompson and Bruckner, 1970) and isolated bullfrog mucosa (Nakajima, 1970) or did not affect gastric acid secretion in rats (Brenna *et al.*, 1993) and dogs (Konturek *et al.*, 1971). Conflicting data have been also reported on the effect of nicotine on gastric mucosal damage. Gastric mucosal damage induced by hypertonic saline, stress or ethanol was aggravated by acute (Endoh *et al.*, 1991) or chronic (Qiu *et al.*, 1992a; Wong and Ogle, 1995) nicotine administration. However, a series of papers reported that acute or chronic nicotine treatment protected gastric mucosa against ethanol-induced gastric mucosal damage (Cho *et al.*, 1990; Endoh *et al.*, 1991, 1992). This controversy may be due to the difference of methods of nicotine administration used in each study, and the state (basal or stimulated) of gastric acid secretion under which nicotine was administered.

This study was performed to elucidate the effect of intermittent administration of nicotine, mimicking human habituation of cigarette smoking, on gastric mucosal damage. For focusing gastric acid secretion as a mechanism of nicotine's action, effects of nicotine on pentagastrin-stimulated gastric mucosal damage and on pentagastrin-induced acid secretion were studied. Gastric perfusion model was used for the study of acid secretion to measure time-based effect of nicotine.

MATERIALS AND METHODS

Animals

Sprague-Dawley rats weighing 200~260 g were used. After 1 week adaptation period, experiments were performed. For the gastric perfusion experiment, rats were fasted for 48 hours but were allowed water *ad libitum*.

Pentagastrin-induced mucosal damage

Rats were divided into 3 groups. Nicotine hydrogen tartrate salt (Sigma Chemical Co., USA) dissolved in saline were administered intragastrically twice per day (0800, 1700) for 9 days. Group 1 received vehicle: saline, Group 2 received 5 mg/kg nicotine, and Group 3 received 10 mg/kg nicotine. Rats were fasted since receiving 0800 administration of nicotine on day 7. On day 9, pentagastrin 1.2 mg/kg (Sigma Chemical Co., USA) was injected subcutaneously 1 hour after 0800 administration of nicotine. Pyloric ligation was done under light ether anesthesia 30 minutes after pentagastrin injection. Six hours after operation, rats were sacrificed by cervical dislocation, and stomach was rapidly removed. Then, gastric juice was collected and measured the volume of juice, free and total acidity. Gastric juice was titrated by pH 3.0 or pH 7.0 for measurement of free acidity or total acidity, respectively. For measurement of gastric mucosal damage, stomach was opened along the greater curvature and the area of damaged mucosa was measured.

Gastric perfusion

Rats were anesthetized by a subcutaneous administration of urethane (1.54 g/kg). Tracheostomy was done, and two polyethylene cannulae were introduced into the stomach for the gastric perfusion system; the esophageal cannula was placed in the cardiac portion through an esophageal incision and the duodenal cannula was placed in the pyloric portion through a duodenal incision. Another polyethylene cannula was inserted into the jugular vein for the administration of drugs. Rats were then allowed to stabilized for one hour after surgery, during which time the stomach was perfused with 4 ml of saline (pH 6.0) every 15 min. The secretion of gastric acid was measured by using the gastric perfusion system. Briefly, 4 ml portions of the perfusion solution were introduced into the stomach as a bolus via the esophageal cannula every 15 min. Samples were collected every 15 minutes from the duodenal cannula and titrated to pH 6.0 with an automatic potentiometric titrator (TTT_2b, Radiometer, Copenhagen, Denmark). Gastric acid output was expressed in μEq/15 min. To study intragastric effect of nicotine, nicotine 5.0 mg/kg was dissolved in 4 ml of perfusion solution and introduced into the stomach and collected the solution via duode-

nal cannula after 30 min. This 30 minstaying solution was discarded and perfusion with 15 min interval was continued. To study the effect of i.v. nicotine, nicotine (0.5 mg/kg, 1.0 mg/kg) was injected through a jugular vein cannula slowly for 10 min. To study the effect of i.v. nicotine on pentagastrin-stimulated acid secretion, pentagastrin (10 μg/kg/hr) was infused continuously through a jugular vein cannula.

Measurement of blood pressure changes

To measure blood pressure, cannula from a common carotid artery was connected to the pressure transducer (Grass Instrument Co. USA) and the signal was amplified and recorded by Model 7 Polygraph system (Grass Instrument Co., USA). Other procedures were the same as those for the gastric perfusion experiment. Pentagastrin or nicotine was administered by the same schedule of the gastric perfusion experiment.

RESULTS

Effect of nicotine on pentagastrin-induced gastric mucosal damage

Pentagastrin plus 6 hours' pyloric ligation produced considerable gastric mucosal damage mainly glandular portion of the stomach. Intermittent treatment of nicotine for 9 days before pentagastrin challenge markedly reduced damaged area about 50% of the control. The degree of protection was similar in both doses of nicotine used in the study (5 mg/kg, 10 mg/kg, twice per day) (Table 1). When examined the accumulated gastric juice after pyloric ligation for 6 hours, nicotine reduced the volume of juice, and free and total acidity (Table 2). Gastric perfusion experiment was performed to confirm whether the reduced acidity came from reduced acid secretion by nicotine.

Effect of intragastric nicotine on the gastric acid secretion

When the stomach was perfused with perfusion solution, the secretion of gastric acid stabilized within 30 minutes and maintained throughout experiment(at least 225 minutes = 15 perfusion period; one perfusion period represents one interval (15 min) of the perfusion) with a fairly stable manner. The basal acid secretion was 3~6 μEq/15min. Intragastric nico-

Table 1. Effects of nicotine on pentagastrin-induced gastric mucosal damage in pylorus-ligated rat

	Lesion area(mm^2)
Saline	19.28±11.93
Nicotine	
5 mg/kg	9.01±4.82*
10 mg/kg	10.54±4.33*

Values are means±S.D. of 10 rats in each group. Saline or intragastric nicotine 5 mg/kg or 10 mg/kg were administrated twice per day for 9 days. Pentagastrin 1.2 mg/kg was injected subcutaneously on day 9 and pyloric ligation was performed. Six hours after pyloric ligation, stomach was removed and examined. *$p<0.05$, vs. the Saline group (Student's t-test).

Table 2. Effects of nicotine on pentagastrin-induced gastric acid secretion in pylorus-ligated rats

	Volume (ml)	Free acid (Eq/l)	Total acid (Eq/l)
Salind	8.02±2.64	96.32±11.90	150.54±12.10
Nicotine			
5 mg/kg	5.33±1.66*	81.29±17.27*	126.28±9.25*
10 mg/kg	4.47±1.84***	68.56±6.77***	123.68±20.74*

Values are means±S.D. of 10 rats in each group. *$p<0.05$, ***$p<0.01$ vs. the Saline group (Student's t-test). Other legends are the same as Table 1.

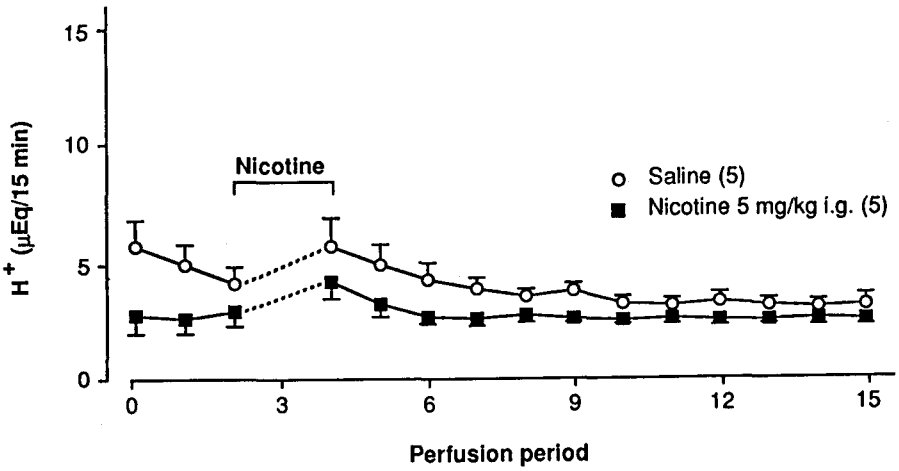

Fig. 1. Effect of intragastric nicotine on acid secretion in perfused rat stomachs. Under urethane anesthesia, 4 ml of saline (pH 6.0) was perfused into the stomach at 15 min intervals. One perfusion period represents one perfusion interval (15 min). Nicotine was administrated with a perfusion solution at a concentration of 5 mg/kg. The nicotine solution existed in the stomach for 30 min (dotted line). Numbers in the parentheses denote the number of animals.

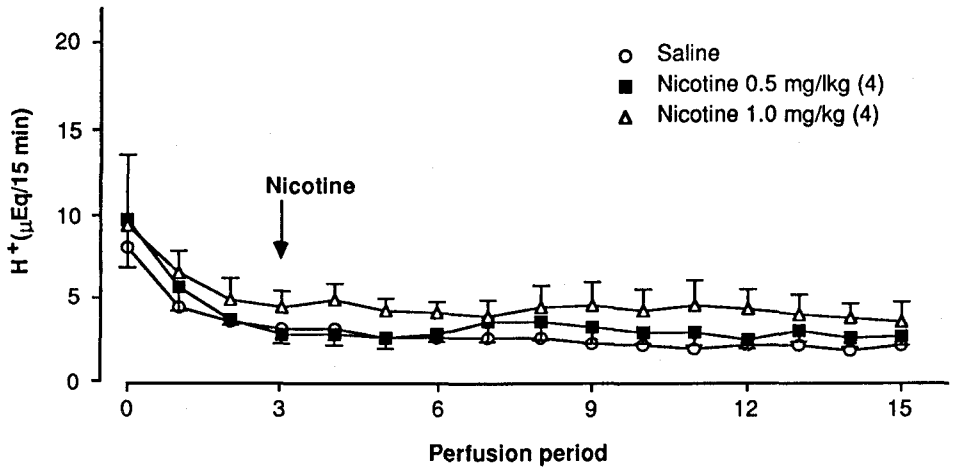

Fig. 2. Effect of intravenous nicotine on acid secretion in perfused rat stomachs. Under urethane anesthesia, 4 ml of saline (pH 6.0) was perfused into the stomach at 15 min intervals. One perfusion period represents one perfusion interval (15 min). A bolus injection of nicotine was done through the jugular vein cannula.

tine resided in the stomach for 30 min at a concentration of 5 mg/kg did not affect basal gastric secretion. The acid secretion of the very next perfusion after intragastric nicotine was slightly increased because the previous perfusion solution, which existed in the stomach for 30 min instead of 15min, has not been fully washed (Fig. 1).

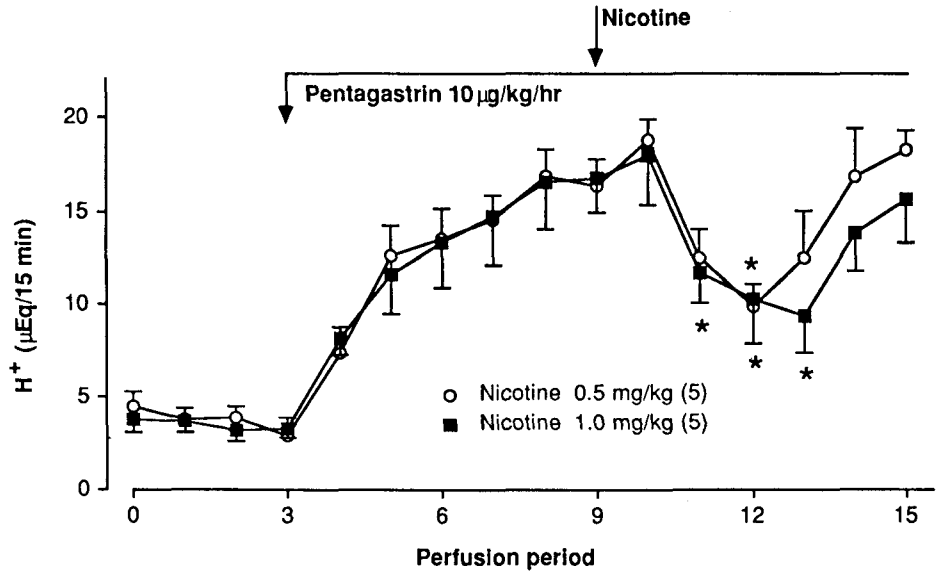

Fig. 3. Effect of intravenous nicotine on gastrin-induced acid secretion in perfused rat stomachs. Under urethane anesthesia, 4 ml of saline (pH 6.0) was perfused into the stomach at 15 min intervals. One perfusion period represents one perfusion interval (15 min). Through a jugular vein cannula, gastrin was infused continuously at a dose of 10 μg/kg/hr, and a bolus injection of nicotine was done. *$p<0.05$, vs. the pre-nicotine level (paired t-test).

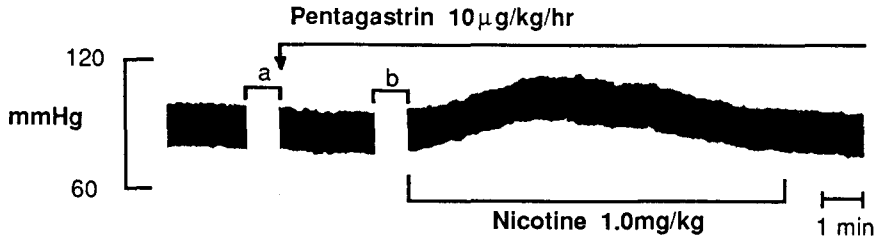

Fig. 4. A representative tracing of blood pressure monitoring from 5 experiments during the gastric perfusion experiment. Blood pressure was monitored through a common carotid artery cannula. (a: 45 min, b: 75 min)

Effect of intravenous nicotine on the gastric acid secretion

Similar to the intragastric nicotine, intravenous administration of nicotine did not affect basal acid secretion in the perfused rat stomach (Fig. 2). For the next step, we tested the effect of nicotine on the pentagastrin-stimulated acid secretion. When acid secretion of the perfused stomach was stabilized, pentagastrin 10 μg /kg/hr was infused continuously. The acid secretion rose quickly after pentagastrin infusion, and the increased acid secretion was stabilized after 4 perfusions at a level of 16~17 μEq/L. After confirming the stable acid secretion for 2 more perfusions, nicotine 0.5 mg/kg or 1.0 mg/kg were administered intravenously for 10 min slowly. The acid secretion decreased from the second perfusion after nicotine and reached the maximum decrease on the third perfusion by

0.5 mg/kg nicotine and on the fourth perfusion by 1.0 mg/kg nicotine. Then, the acid secretion recovered to the pre-nicotine gastrin-stimulated level. This inhibitory effect of nicotine on the gastrin-induced acid secretion was dose-related. The maximum decrease in acid secretion by 0.5 mg/kg nicotine was 41% and by 1.0 mg/kg nicotine was 45% of the pre-nicotine level, and the recovery after 0.5 mg/kg nicotine was faster than that of 1.0 mg/kg nicotine.

Effect of nicotine on the blood pressure

To elucidate an involvement of autonomic effect of nicotine on the inhibition of gastrin-stimulated acid secretion, changes of blood pressure was measured under the same situation of gastric perfusion experiment. Transient slight increase in blood pressure was noted during a period (10 min) of a bolus injection of nicotine. The maximum effect ($105.0 \pm 6.6/80.6 \pm 7.2$ mmHg) appeared 4~5 min after beginning of the nicotine injection, and the blood pressure recovered to the pre-nicotine level ($99.2 \pm 10.0/76.4 \pm 1.8$ mmHg) within 10 min.

DISCUSSION

Results of this study clearly showed nicotine's protective effect on gastric mucosal damage. Two opposite lines of reports has been published. One claimed that nicotine protected gastric mucosal damage, and the other claimed that nicotine aggravated gastric mucosal damage. With the epidemiologic study, the majority of papers concerned with hazardous effect of nicotine. However, Endoh *et al.* (1991, 1992, 1993) reported, recently, a series of results in which nicotine protected gastric mucosa against ethanol-induced gastric injury. They gave a bolus of intragastric nicotine (4 mg/kg) intragastrically 1 hour before applying intragastric 40% ethanol. From this schedule of experiment, they observed reduction of the lesion score more than 50% of the control. This observation has been extended to examine the mechanism of nicotine protection, and they suggested that activation of α_2-adrenoceptors was involved in the protective effect of intragastric nicotine possibly by production of mucus.

Unlike this observation, Ogle's group serially reported nicotine's hazardous effect on ethanol- or stress-induced gastric mucosal damage (Wong *et al.*, 1986; Qiu *et al.*, 1992a; Qiu *et al.*, 1992b; Wong and Ogle, 1995). They extended these observation to examine the mechanism of nicotine-induced aggravation, and suggested that nicotine caused the sensitization of muscarinic receptors which could potentiate gastric aggressive factor: acid.

The first difference of two opposite series of reports is the nature of stress applied to the experimental animals. The mechanism of stress-induced gastric mucosal damage is clearly different from that of ethanol-induced gastric mucosal damage. However, when Wong and Ogle (1995) applied intragastric 40% ethanol, the same dose of Endoh's experiments, they observed that nicotine aggravated ethanol-induced gastric mucosal damage. The second difference of these two series of reports is the method of administration of nicotine. In nicotine-induced protection case, a bolus of intragastric nicotine was used. However, in nicotine-induced aggravation case, Ogle's group used chronic continuous delivery of nicotine for 10~15 days by using methods of ingestion from drinking tap water or of implanting osmotic pump. This difference of methods for applying nicotine may be the key factor. Battistel *et al.* (1993) also showed nicotine-induced vascular dysregulation in the rat gastric mucosa when nicotine was given through tap water for 50 days. Delivery of nicotine via tap water drinking may be one of the methods of continuous administration. Although the authors did not specify the amount of tap water consumed, it is possible that animals drank tap water according to the body concentration of nicotine when considering abuse liability of nicotine (Henningfield *et al.*, 1995). On the other hand, intermittent smoking lowered acid secretion induced by modified sham feeding in human study. In the present study, we gave intragastric nicotine intermittently for 9 days, and observed nicotine-induced protection against gastrin-induced gastric mucosal damage in pylorus-ligated rats. The schedule of nicotine administration we used was not a continuous delivery of nicotine. Our

finding and others' results suggests that the intermittent or single bolus administration of nicotine protects gastric mucosa from noxious stimuli, but a continuous administration of nicotine aggravates gastric mucosal damage. Protective effect of nicotine was not dose-related and the degree of protectron was not complete in the present study. These findings suggest that the protection is not due to the direct effect of nicotine and/or is not sufficient to prevent gastric mucosa against noxious stimuli. Therefore, it is also suggested that chronic intermittent administration of nicotine somehow stimulates natural body defense mechanisms of gastric mucosa.

To examine the mechanism of action of protective effect of nicotine on the high dose of gastrin-induced mucosal damage, we performed gastric perfusion experiment. The basal acid secretion did not affect by a bolus administration of nicotine intragastrically or intravenously. However, gastrin-stimulated acid secretion markedly reduced by a single bolus injection of nicotine, and the response was dose-related and reversible. These results are compatible with other reports in which rats were used as experimental animals. Brenna *et al.* (1993) reported that intravenous nicotine did not affect basal acid secretion and histamine release in the an isolated perfused rat stomach. Similarly, Leung (1994) reported that intravenous nicotine did not affect basal acid secretion in rats by 4 or 40 μg/kg/min infusion for 45 min, but these doses of nicotine completely inhibited pentagastrin-stimulated acid secretion. In human, similar to the results from animals, basal gastric acidity was not affected by nicotine given by nasal spray (Lindell *et al.*, 1992), and the increased plasma gastrin concentration induced by modified sham feeding decreased in the smoking day (Lindell *et al.*, 1993). Therefore, results from rats can be postulated to human, and our results demonstrated that decreased acid secretion is an important factor of nicotine-induced protection against gastrin-induced gastric mucosal damage.

Nicotine has a well-known autonomic effects. If a bolus injection of nicotine caused ganglionic blocking effect, blood pressure should be decreased similar to hexamethonium or mecamylamine (Endoh *et al.*, 1992). These ganglionic blocking agents showed protective effect against 40% ethanol-induced gastric mucosal damage. The lowered blood pressure may have an influence on the protective effect of these agents although the authors did not mention about it. In the present study, we monitored blood pressure along with the gastric perfusion experiment to examine the effect of nicotine on blood pressure. The results of this experiment indicated that the effect of nicotine on the inhibition of acid secretion is not related to the changes of blood pressure, since gastric acid secretion decreased from the second perfusion period after nicotine while nicotine-induced peak increase in blood pressure was noted at 4~5 min after the beginning of nicotine injection and recovered to the pre-nicotine level within 10 min.

In conclusion, the present study clearly indicates that chronic intermittent administration of nicotine protects gastric mucosa against gastrin-induced gastric mucosal damage, and nicotine inhibits gastrin-induced acid secretion. Although many evidences supports nicotine's harmful effect on the gastric mucosa (for review, Endoh and Leung, 1994), the present study strongly suggests that the methods of administration of nicotine is an important factor of the divergence of nicotine's action on the gastric mucosa.

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=국문초록=

Gastrin 유발 위점막 손상에 대한 Nicotine의 보호 효과

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위점막 손상에 미치는 영향에 관한 nicotine의 효과는 아직 정설이 없는 형편이다. 본 연구에서는 nicotine이 위점막 손상에 미치는 영향을 보기 위하여 nicotine (5 mg/kg, 10 mg/kg)을 9일간 하루에 두번씩 위내 투여하였다. 위점막 손상은 gastrin (1.2 mg/kg)을 피하 주사함과 동시에 유문부결찰을 6시간 동안 시행하므로 야기시켰다. 그 결과 nicotine 투여군에서 현저한 위점막 손상의 감소를 보였다 (대조군의 50%). 이러한 nicotine의 위점막 보호 효과에 대한 기전을 추구하기 위하여 위관류 실험을 시행하였다. Nicotine은 기초 위산 분비에는 영향이 없었으나 gastrin으로 자극된 위산 분비를 현저히 감소시켰고, 이러한 반응은 nicotine 용량에 비례하였다. 이상의 결과로 보아 nicotine의 장기간 간헐적 투여는 gastrin 투여로 인한 위점막 손상에 보호 효과가 있으며, 이러한 효과는 gastrin으로 자극된 위산 분비를 억압하는 nicotine의 효과가 관련될 것으로 생각된다. 또한 nicotine의 위점막 손상 악화 효과를 관찰한 보고들을 고려하면 nicotine의 위점막 손상에 관한 효과는 nicotine의 투여 방법에 따라 전혀 다르게 나타날 수 있을 것으로 생각된다.