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Effects of Nicotine on Activity and Stress-Induced Gastric Ulcers in Rats

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QIU, B. S., C. H. CHO AND C. W. OGLE. *Effects of nicotine on activity and stress-induced gastric ulcers in rats.* PHARMACOL BIOCHEM BEHAV **43**(4) 1053–1058, 1992.—Nicotine is known to influence locomotor activity. The alkaloid also intensifies gastric ulcer formation in stressed rats. The effects of nicotine on locomotor activity in relation to gastric lesions induced by restraint at 4°C for 2 h (stress) were, therefore, studied. Ten-day treatment with nicotine 25 or 50 μg/ml drinking water potentiated stress-evoked ulceration and mast cell degranulation. These same doses of nicotine increased vertical motor activity; only the higher dose of the alkaloid enhanced horizontal movements. Phenobarbitone (12.5, 25, or 50 mg/kg, SC) dose dependently reduced vertical activity, as well as stress-induced gastric ulceration and mucosal mast cell degranulation. The drug also lessened the potentiating effects of nicotine on motor activity and stress-evoked gastric lesion formation. It is concluded that the ability of chronic nicotine treatment to intensify stress-induced gastric ulceration most likely owes part of its action to a mechanism evoking increased activity, which possibly reflects an influence on the CNS, as well as to enhancement of mast cell degranulation in the stomach glandular mucosa.

Gastric ulceration Mast cells Locomotor activity Nicotine Phenobarbitone Rats

CHRONIC nicotine treatment worsens gastric mucosal damage evoked by restraint at 4°C for 2 h (stress) in rats (20,21). It is known that chronic treatment with the alkaloid influences locomotor activity (9,14,29). Paré reported that oral administration of nicotine increased activity-stress ulcers in rats (18); however, the relationship between the effects of nicotine on ulcer formation and locomotor activity is still not clear. It is possible that mechanisms other than those in the stomach itself, possibly reflected by the degree of locomotor activity, may be responsible for at least some of its ulcer-intensifying actions in stressed rats. More insight into the pathophysiology of this phenomenon is important because there is a tendency to smoke more under stressful conditions, and nicotine is a major component of tobacco (2).

It has been demonstrated that phenobarbitone, which depresses the CNS (4), can reduce both behavioral activity and cold-restraint stress-evoked gastric ulceration in rats (11). This barbiturate was, therefore, used in the current study to evaluate the relationship, if any, between the action of nicotine on nervous activity and its ability to potentiate stress-induced gastric lesions. Mast cell degranulation, a major gastric ulcerogenic factor in stress (26), is believed to be vagal mediated (13). The degree of gastric mucosal mast cell degranulation under different experimental conditions was, therefore, also examined.

METHOD

General

Female Sprague-Dawley rats (150–170 g) (a total of 389 was used in this study) were kept in an air-conditioned room (22 ± 1°C, humidity 65–70%) and allowed free access to a normal rat laboratory pellet diet (Purina, Ralston Co.). Animals drank either ordinary tapwater (controls) or a solution of nicotine bitartrate (Sigma Chemical Co., St. Louis, MO) 25 or 50 μg/ml tapwater; all groups were permitted to drink ad lib for 8 days. Rats were then fasted for 48 h prior to experimentation, when they were housed in cages with raised wire-mesh floors to prevent coprophagy and given 8% sucrose in 0.2% NaCl w/v to drink; in the case of alkaloid-treated rats, their sucrose-salt solutions contained the same concentrations of nicotine. All drinking solutions were removed 1 h before experiments. In the activity-measuring experiments, a total of 96 rats (8 animals per group) were used. In gastric ulcer and mucosal mast cell count experiments, 293 rats were used in groups of 10–14 animals.

Gastric Ulceration Induced by Cold-Restraint Stress

The method of cold-restraint stress for producing gastric lesions was that of Senay and Levine (28). Rats were divided into two batches; one group was restrained in individual close-fitting tubular wire-mesh cages and exposed to a room temperature of 4°C; animals in the other batch, acting as controls, were left in their starvation cages at 22°C. After 2 h, all animals were killed by a sharp blow on the head and their stomachs removed for examination.

Measurement of Gastric Mucosal Lesions

The severity of mucosal lesions was determined under an illuminated magnifier (3×). Lesion size (mm) was measured

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along its greatest length; in the case of petechiae, five such lesions were considered the equivalent of a 1-mm ulcer. The sum of the lesion lengths in each group of animals was divided by its number and expressed as the mean ulcer index (6).

Examination of Gastric Mucosal Mast Cells

The method of staining and determining the number of mast cells in the gastric mucosa was similar to that used by Cho and Ogle (6).

The glandular portion of the stomach, immediately after examination for mucosal lesions, was fixed in freshly prepared 4% w/v lead acetate (E. Merck, Darmstadt, Germany) solution. Following a 48-h fixation period, the tissue was dehydrated with alcohol, cleared with xylene, and embedded in paraffin ("tissue prep"; Fisher Scientific Co., Fair Lawn, NJ). Sections were then made by cutting the paraffin block in a plane vertical to the mucosal surface of the tissue; these were mounted and stained with an aqueous solution of toluidine blue (Sigma, St. Louis, MO). The mast cell count was expressed as the number of granulated metachromatically stained mast cells seen in 42 adjacent oil immersion (magnification 1,000×) fields in an area immediately below and parallel to the surface epithelium of the mucosa.

Locomotor Activity Measurements

An animal activity-monitoring system (constructed by the Electronic Services Unit, University of Hong Kong) was used to evaluate locomotor activity. The monitor, utilizing infrared light and video cameras, recorded locomotor activity in a computer (IBM PC/AT); the horizontal pattern of movement, as well as the jumping and rearing activities of four animals, each in a separate chamber (length 350 mm, width 245 mm, depth 430 mm), were recorded simultaneously.

Before starting measurements, all animals were placed individually in their motor activity chambers for 30 min to allow them to familiarize themselves with their surroundings. They were then observed from 0900–1100 h daily. Rats were only used once for these experiments. The following three variable parameters—a)speed of horizontal movement (mm/s), b) vertical rearing (for a minimum period of 200 ms), and c) jumping (when all four paws of the animal were simultaneously not in contact with the floor, either when leaping up from the rearing position or jumping up from a prone posture)—were examined. All testing was carried out under simulated daylight conditions, with controlled temperature and humidity; the room was soundproofed. Data were analyzed at 15-min intervals.

Drugs

Phenobarbitone sodium (Bayer, A. G., Leverkusen, Germany) was freshly prepared in 0.9% NaCl w/v in distilled water (saline) and the doses expressed as bases. The barbiturate was injected SC 30 min before starting experiments. A similar volume of saline (2 ml/kg) was given by the same route to controls.

Statistical Analysis

The results were expressed as means ± SE. Data were analyzed by the two-tailed Student's *t*-test. Differences between groups exposed to the same experimental conditions were also analyzed by mixed analysis of variance (ANOVA). Fisher's

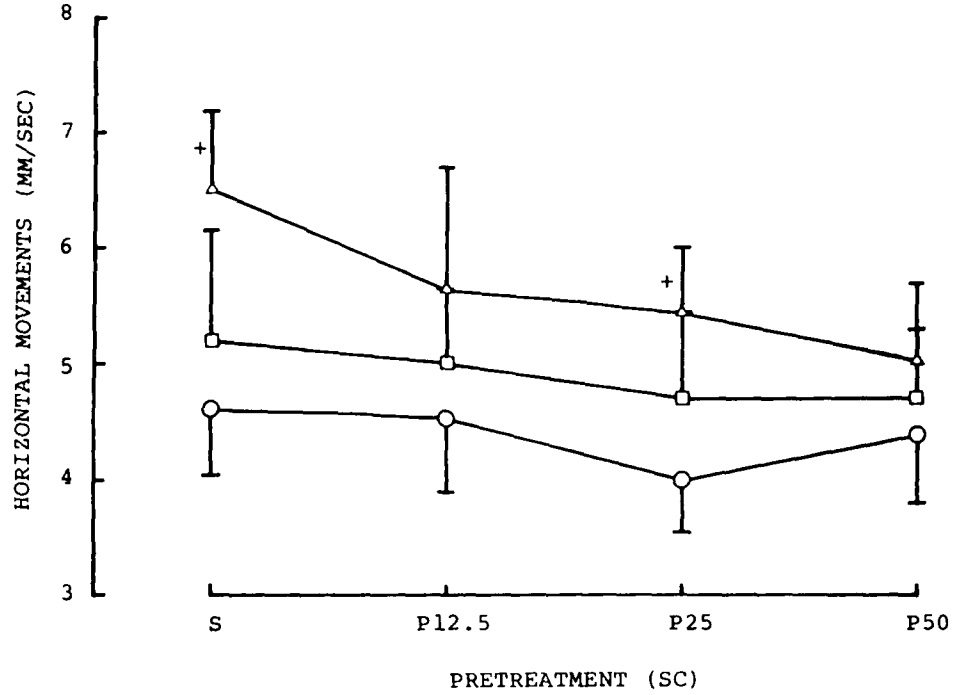

FIG. 1. Effects of nicotine and/or phenobarbitone on horizontal movements. (○), tap water; (□), nicotine 25 μg/ml × 10 days; (△), nicotine 50 μg/ml × 10 days. S, saline (1 ml/kg, SC); P, phenobarbitone (mg/kg, SC). Values are means ± SE of eight rats in each group. $^{+}p < 0.05$ when compared to the corresponding value of the tapwater-drinking control

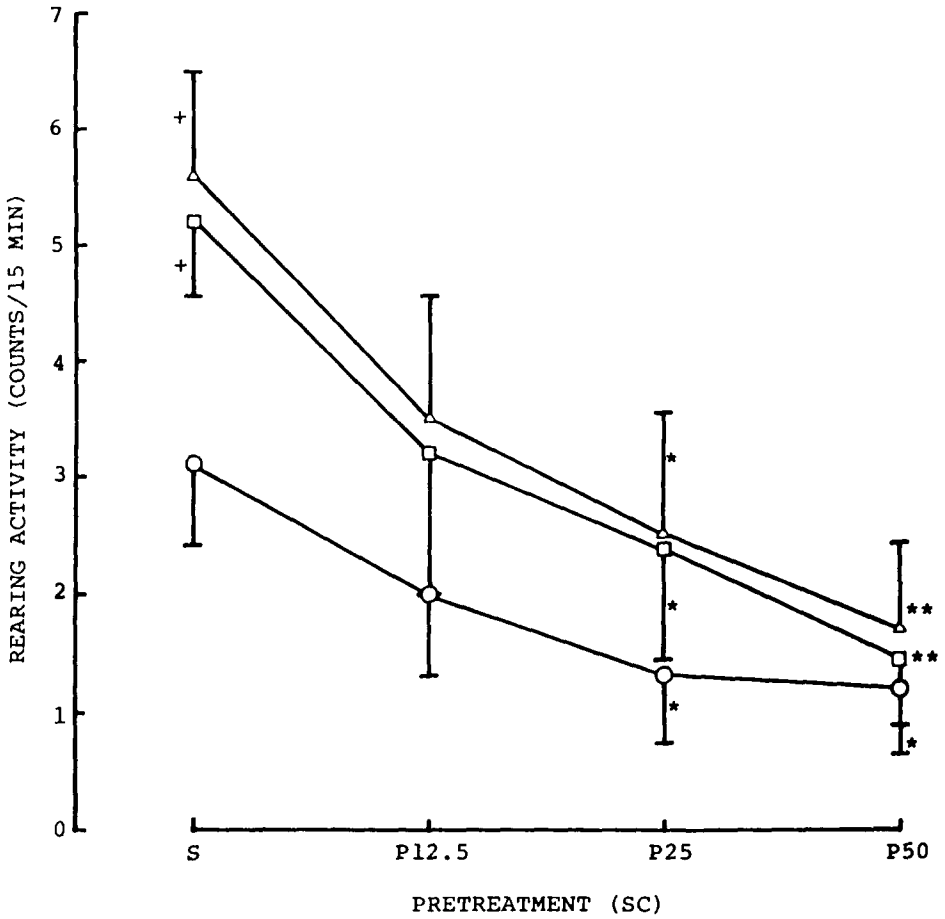

FIG. 2. Effects of nicotine and/or phenobarbitone on rearing activity. (○), tapwater; (□), nicotine 25 μg/ml × 10 days; (△), nicotine 50 μg/ml × 10 days. S, saline (2 ml/kg, SC); P, phenobarbitone (mg/kg, SC). Values are means ± SE of eight rats in each group. $^{*}p < 0.05$, $^{**}p < 0.01$ when compared to its own saline-pretreated control; $^{+}p < 0.05$ when compared to the corresponding value of the tapwater-drinking control.

TABLE 1

EFFECTS OF PHENOBARBITONE (INJECTED SC 30 min BEFORE) ON STRESS-INDUCED GASTRIC ULCERS AND MAST CELL DEGRANULATION IN RATS DRINKING TAPWATER

Treatment	No. of Rats With Petechiae and/or Hemorrhagic Ulcers	Ulcer Index (mm)	Mucosal Mast Cell count/42 o.i.f.
A. No stress (unrestrained at 22°C for 2 h)			
0.9% Saline 2 ml/kg	5 (14)	0.09 ± 0.04	65 ± 6.5
Phenobarbitone 12.5 mg/kg	3 (14)	0.06 ± 0.04	64 ± 5.9
Phenobarbitone 25.0 mg/kg	4 (14)	0.06 ± 0.03	62 ± 6.3
Phenobarbitone 50.0 mg/kg	3 (14)	0.04 ± 0.02	63 ± 6.6
B. Stress (restrained at 4°C for 2 h)			
0.9% Saline 2 ml/kg	13 (13)*	6.19 ± 0.85†	44 ± 4.5‡
Phenobarbitone 12.5 mg/kg	13 (13)*	5.04 ± 0.63†	47 ± 5.1§
Phenobarbitone 25.0 mg/kg	13 (13)*	3.39 ± 0.94†¶	51 ± 5.3
Phenobarbitone 50.0 mg/kg	9 (12)*	2.02 ± 0.67*#	59 ± 5.2¶

Values are expressed as means ± SE. Number of rats in each group in parentheses. o.i.f., oil immersion field (1,000 ×).

$^{*}p < 0.01$, $^{\dagger}p < 0.001$, $^{\ddagger}p < 0.02$, $^{\S}p < 0.05$, when compared to its own corresponding group in A.

$^{\P}p < 0.05$, $^{\#}p < 0.01$ when compared to its own control in B.

TABLE 2

EFFECTS OF PHENOBARBITONE (INJECTED SC 30 min BEFORE) ON STRESS-INDUCED GASTRIC ULCERS AND MAST CELL DEGRANULATION IN RATS DRINKING NICOTINE SOLUTION (25μg/ml) FOR 10 DAYS

Treatment	No. of Rats With Petechiae and/or Hemorrhagic Ulcers	Ulcer Index (mm)	Mucosal Mast Cell count/42 o.i.f.
A. No stress (unrestrained at 22°C for 2 h)			
0.9% Saline 2 ml/kg	2	0.07 ± 0.05	68 ± 8.5
Phenobarbitone 12.5 mg/kg	3	0.06 ± 0.03	65 ± 7.3
Phenobarbitone 25.0 mg/kg	2	0.05 ± 0.04	67 ± 8.7
Phenobarbitone 50.0 mg/kg	2	0.08 ± 0.06	64 ± 7.1
B. Stress (restrained at 4°C for 2 h)			
0.9% Saline 2 ml/kg	10*	9.40± 1.14†	42 ± 5.3‡
Phenobarbitone 12.5 mg/kg	10*	7.05 ± 0.85†	45 ± 4.1§
Phenobarbitone 25.0 mg/kg	10*	5.20 ± 1.27†¶	52 ± 4.7
Phenobarbitone 50.0 mg/kg	10*	3.70 ± 0.94†#	58 ± 5.3¶

Values are expressed as means ± SE of 10 rats in each group. o.i.f., oil immersion field (1,000 ×).
*$p < 0.01$, †$p < 0.001$, ‡$p < 0.02$, §$p < 0.05$, when compared to its own corresponding group in A.
¶$p < 0.05$, #$p < 0.01$ when compared to its own control in B.

exact test was used to examine differences between groups for mucosal lesion incidence.

RESULTS

Effects of Nicotine and/or Phenobarbitone on Horizontal Activity

Ten-day treatment with nicotine tended to increase the horizontal movements and significance ($p < 0.05$) was reached with saline-pretreated rats drinking nicotine 50 μg/ml tapwater (Fig. 1). Phenobarbitone (12.5, 25, or 50 mg/kg), injected SC 0.5 h beforehand, did not significantly influence the horizontal movements in both controls and nicotine-treated animals. The significant increase ($p < 0.05$) in movements seen with nicotine 50 μg/ml was still present in the group pretreated with phenobarbitone 25 mg/kg.

Effects of Nicotine and/or Phenobarbitone on Vertical Activity

Figure 2 shows the effects of nicotine and/or phenobarbitone on rat rearing activity. Ten-day treatment with nicotine 25 or 50 μg/ml increased rearing activity [ANOVA, $F(2, 84) = 3.5$, $p < 0.05$]. Phenobarbitone dose dependently decreased vertical activity [ANOVA, $F(3, 84) = 8.9$, $p < 0.005$]. The interaction values between nicotine- and phenobarbitone-treated groups and between individual animals in these groups were not significantly different. Both doses of nicotine significantly increased vertical activity in saline-pretreated rats when compared to the tapwater control (both $p < 0.05$); the two higher doses of phenobarbitone significantly decreased vertical activity in both nicotine- and tapwater-drinking animals (all $p < 0.05$). The average number of jumps in each 15-min period was small and was comparable

TABLE 3

EFFECTS OF PHENOBARBITONE (INJECTED SC 30 min BEFORE) ON STRESS-INDUCED GASTRIC ULCERS AND MAST CELL DEGRANULATION IN RATS DRINKING NICOTINE SOLUTION (50μg/ml) FOR 10 DAYS.

Treatment	No. of Rats With Petechiae and/or Hemorrhagic Ulcers	Ulcer Index (mm)	Mucosal Mast Cell count/42 o.i.f.
A. No stress (unrestrained at 22°C for 2 h)			
0.9% Saline 2 ml/kg	6 (14)	0.13 ± 0.04	64 ± 6.6
Phenobarbitone 12.5 mg/kg	4 (13)	0.09 ± 0.04	67 ± 5.5
Phenobarbitone 25.0 mg/kg	4 (13)	0.09 ± 0.05	61 ± 5.0
Phenobarbitone 50.0 mg/kg	3 (14)	0.05 ± 0.03	62 ± 6.0
B. Stress (restrained at 4°C for 2 h)			
0.9% Saline 2 ml/kg	13 (13)*	14.70 ± 2.23†	32 ± 3.5†
Phenobarbitone 12.5 mg/kg	13 (13)*	13.10 ± 1.81†	34 ± 3.3†
Phenobarbitone 25.0 mg/kg	12 (12)*	8.23 ± 1.64†‡	46 ± 3.9†§
Phenobarbitone 50.0 mg/kg	14 (14)*	6.21 ± 0.92†¶	55 ± 5.3¶

Values are expressed as means ± SE. Number of rats in each group in parentheses. o.i.f., oil immersion field (1,000 ×).
*$p < 0.01$, †$p < 0.001$, §$p < 0.05$, when compared to its own corresponding group in A.
‡$p < 0.05$, ¶$p < 0.01$ when compared to its own control in B.

between the various groups (tapwater; 0.9 ± 0.48; nicotine 25 μg/ml, 0.6 ± 0.4; nicotine 50 μg/ml, 0.3 ± 0.55). In this study, the jumps recorded were due to animals rearing up and then leaping to reach higher up the chamber wall.

Effects of Phenobarbitone and/or Nicotine on Stress-Induced Ulcers and Mast Cell Degranulation

Tables 1-3 show the effects of phenobarbitone on stress-induced gastric ulceration and mucosal mast cell counts in rats drinking tapwater or nicotine solutions. The mean ulcer indices and glandular mucosal mast cell counts in tapwater- (Table 1A) or nicotine-treated (Tables 2A and 3A) animals were similar in nonstressed conditions, irrespective of the alkaloid doses; these two parameters were also not altered by phenobarbitone treatment (Tables 1-3). Cold-restraint stress for 2 h produced hemorrhagic ulcers (Tables 1B, 2B, and 3B; all $p < 0.01$) and lowered the mast cell counts (all $p < 0.02$) in the glandular mucosa. All stressed animals whether injected with saline or phenobarbitone showed a 100% incidence of lesions in the glandular mucosa except the tapwater-drinking controls given the highest pretreatment dose of phenobarbitone (Table 1B), but the difference was not significant.

Nicotine worsened stress-evoked ulceration in a dose-dependent manner [Tables 1-3; ANOVA, $F(2, 131) = 28$, $p < 0.005$]. Phenobarbitone dose dependently antagonized stress-induced gastric ulceration in rats given tapwater or nicotine [Tables 1-3; ANOVA, $F(3, 131) = 14$, $p < 0.005$]. The interaction values between nicotine- and phenobarbitone-treated groups and between individual rats in these groups were also not significantly different. Phenobarbitone 25 or 50 mg/kg also prevented mast cell degranulation in stressed animals given either tapwater or nicotine (Tables 1-3). Nicotine treatment with the higher concentration of 50 μg/ml drinking tapwater potentiated stress-evoked mast cell degranulation (Tables 1 and 3).

DISCUSSION

It has been reported that rats with high activity tend to develop activity-stress ulcers more easily than those exhibiting low activity (19). Although it has been shown that nicotine increases rat locomotor activity (7), and can augment activity-stress ulcer formation (18), it is still unclear whether the effects of nicotine on activity and stress-evoked gastric mucosal damage are related.

Chronic nicotine treatment, with amounts comparable to the daily intake of the alkaloid in heavy smokers (12,15), increased both horizontal and vertical activities in rats. It was found that phenobarbitone was able to antagonize vertical but not horizontal movements (Figs. 1 and 2). As hexamethonium, a quaternary ammonium ganglion blocker, only facilitates horizontal activity in rats (25), this suggests that the increased horizontal movements by chronic nicotine treatment could be due to ganglionic blockade of motor inhibitory neurones in the peripheral nervous system. Thus, it is possible that rearing activity may be CNS related, whereas horizontal movements are due to involuntary actions controlled by the peripheral nervous system. The ability of phenobarbitone pretreatment to decrease vertical activity and stress-evoked ulceration in tapwater-drinking rats is, therefore, likely to be due to its known central sedative effect (4). Because the drug also attenuated the potentiating effects of nicotine on rearing activity and stress-induced ulcer formation, this suggests that the action of nicotine on this aspect of locomotor activity could be indicative of a mechanism in the CNS that influences the observed gastric ulceration. This idea is supported by findings that increased stimulation of the CNS by nicotine is functionally linked with enhanced locomotor activity (14). The CNS is also involved in the genesis of stress-induced gastric ulceration (1,3,8,27). Increased vertical activity may, therefore, indicate that CNS stimulation by nicotine may be partly responsible for its ability to worsen stress-evoked ulcers. As the ulcer-intensifying action of nicotine was partially abolished by phenobarbitone, although the latter drug lowered vertical activity to a subnormal level (Fig. 2), it is likely that nicotine in addition has direct actions on the stomach, for example, reducing gastric mucus content (32) and increasing gastric muscarinic receptor sensitivity (22).

It is known that the higher centers in the brain can influence physiological functions of the body through the autonomic nervous system and hormonal secretion and the stomach has been shown to be affected by stress (31). Experimental evidence suggests that stress-evoked gastric ulceration results from the central activation of both the cholinergic (5) and adrenergic (10) systems. A centrally mediated cholinergic factor is, however, thought to be the main pathologic factor in this type of lesion formation (30). The vagal fibers appear to innervate the mast cells and are responsible for their degranulation (13,23), a major factor involved in stress-induced glandular ulcer formation in rats (16,17,24). In the present study, phenobarbitone lowered the severity of both stress-induced gastric ulceration and mast cell degranulation whereas nicotine produced the opposite effects. However, the effect on mast cell degranulation can only partially explain the antiulcer action of phenobarbitone, as well as the adverse influence of nicotine on ulcer formation, because stomachs with normal mast cell counts still showed a considerable number of glandular mucosal lesions. Nevertheless, the results suggest that there is a strong relationship between stress-induced stimulation of the higher centers and gastric mucosal mast cell degranulation and ulcer formation.

In summary, the present study demonstrates an association between the potentiating effects of nicotine on locomotor activity and stress-induced gastric ulcer formation and mast cell degranulation. These actions possibly result from activation of the higher centers, because they are inhibited by phenobarbitone. The findings, thus, further suggest that a contributory ulcerogenic action of nicotine, possibly due to CNS stimulation, operates in addition to its direct detrimental effects on the stomach through mucus reduction and increased muscarinic receptor sensitivity in the organ (22,32).

REFERENCES

1. Alp, M. H.; Court, J. H.; Kerr Grant, A. Personality pattern and emotional stress in the genesis of gastric ulcer. Gut. 11:773-777; 1970.
2. Benowitz, N. L. Clinical pharmacology of nicotine. Annu. Rev. Med. 37:21-32; 1986.
3. Bhargava, K. P.; Daas, M.; Gupta, G. P.; Gupta, M. B. Study of central neurotransmitters in stress-induced gastric ulceration in albino rats. Br. J. Pharmacol. 68:765-772; 1980.
4. Bowman, W. C.; Rand, M. J. Barbitone. In: Textbook of pharmacology. 2nd ed. London: Blackwell; 1980:8.3-8.9.

5. Brodie, D. A.; Hanson, H. M. A study of the factors involved in the production of gastric ulcers by the restraint technique. Gastroenterology 38:353-360; 1960.
6. Cho, C. H.; Ogle, C. W. A correlative study of the antiulcer effects of zinc sulphate in stressed rats. Eur. J. Pharmacol. 48: 97-105; 1978.
7. Clarke, P. B. S. Chronic central nicotine blockade after a single administration of the bisquaternary ganglion-blocking drug chlorisondamine. Br. J. Pharmacol. 83:527-535; 1984.
8. Feldman, S.; Birnbaum, D.; Behar, A. J. Gastric secretion and acute gastroduodenal lesions following hypothalamic and peptic stimulation. An experimental study in cats. J. Neurosurg. 18:661; 1961.
9. Fung, Y. K.; Lau, Y. S. Receptor mechanisms of nicotine-induced locomotor hyperactivity in chronic nicotine-treated rats. Eur. J. Pharmacol. 152:263-271; 1988.
10. Gordon, R.; Sector, S.; Sjoerdsma, A.; Udenfriend, S. Increased synthesis of norepinephrine and epinephrine in the intact rat during exercise and exposure to cold. J. Pharmacol. Exp. Ther. 153: 440-447; 1966.
11. Gupta, M. B.; Nath, R.; Gupta, G. P.; Bhargava, K. P. A study of the anti-ulcer activity of diazepam and other tranquillosedatives in albino rats. Clin. Exp. Pharmacol. Physiol. 12:61-66; 1985.
12. Jarvis, L. R.; Whitehead, R. Effect of nicotine on the morphology of the rat's gastric mucosa. Gastroenterology 78:1488-1494; 1980.
13. Koo, A.; Liu, H. C. Cholinergic innervation of the dog gastric microcirculation. In: Koo, A.; Lam, S. K.; Smaje, L. H., eds. International Symposium on Microcirculation of the Alimentary Tract. Singapore: World Scientific; 1983:105-114.
14. Ksir, C.; Hakan, R.; Hall, D. P., Jr.; Kellar, K. J. Exposure to nicotine enhances the behavioral stimulant effect of nicotine and increases binding of [^{3}H]acetylcholine to nicotine receptors. Neuropharmacology 24:527-531; 1985.
15. Moody, P. M.; Griffith, R. B.; Averitt, J. H. Proceedings of the University of Kentucky Tobacco and Health Research Institute. Tobacco and Health Workshop Conference, Conference Reports 3, Lexington, KY, 1972.
16. Ogle, C. W.; Cho, C. H. Observation on the influence of graded pretreatment doses of zinc sulphate on the gastric effects of reserpine in rats. Pharmacol. Res. Comm. 10:325-335; 1978.
17. Ogle, C. W.; Cho, C. H. Gastric mast cell degranulation in reserpine-induced ulcers in rats: The effect of bilateral vagotomy. IRCS Med. Sci. 7:152; 1979.
18. Paré, W. P. Oral nicotine ingestion and incidence of activity-stress ulcer in the rat. Biochem. Med. 14:51-56; 1975.
19. Paré, W. P. The influence of food consumption and running activity on the activity-stress ulcer in the rat. Digest. Dis. 20:262-273; 1975.
20. Qiu, B. S.; Cho, C. H.; Ogle, C. W. Does nicotine influence stress-induced gastric ulcers? Digestion 49:22-23; 1991.
21. Qiu, B. S.; Cho, C. H.; Ogle, C. W. Chronic nicotine treatment intensifies gastric ulceration by cold-restraint stress in rats. Agents Actions 33:367-371; 1991.
22. Qiu, B. S.; Cho, C. H.; Ogle, C. W. The influence of nicotine on gastric ulceration induced by cold-restraint stress in rats. Abstracts of the 6th Southeast Asian and Western Pacific Regional Meeting of Pharmacologists, Hong Kong, June 30-July 4, 1991, p. 123.
23. Radke, R.; Stach, W.; Weiss, R. Innervation of the gastric wall related to acid secretion: A light and electron microscopy study on rats, rabbits and guinea pigs. Acta. Biol. Med. Ger. 39:687-696; 1980.
24. Räsänen, T. The role of the mucosal mast cells in gastric ulceration. In: Pfeiffer, C. J., ed. Peptic ulcer. Philadelphia, PA: J. B. Lippincott; 1971:237-243.
25. Rodgers, R. J. Effects of nicotine, mecamylamine and hexamethonium on shock-induced fighting, pain reactivity, and locomotor behaviour in rats. Psychopharmacology (Berl.) 66:93-98; 1979.
26. Schwartz, J. C. Gastric histamine in the pathogenesis of experimental ulcers. In: Pfeiffer, C. J., ed. Peptic ulcers. Philadelphia, PA: J. B. Lippincott; 1971:190-198.
27. Sen, R. N.; Anand, B. K. Effect of electrical stimulation of the hypothalamus on gastric secretion activity and ulceration. Ind. J. Med. Res. 45:507-513; 1957.
28. Senay, E. C.; Levine, R. J. Synergism between cold and restraint for rapid production of stress ulcer in rats. Proc. Soc. Exp. Biol. Med. 124:1221-1223; 1967.
29. Silvette, H.; Hoff, E. C.; Larson, P. S.; Haag, H. B. The actions of nicotine on central nervous system functions. Pharmacol. Rev. 14:137-173; 1962.
30. Takagi, K.; Okabe, S. Studies of the mechanisms involved in the production of stress-atropine ulcers in rats. Eur. J. Pharmacol. 10:378-384; 1970.
31. Wolf, S. The psyche and the stomach. Gastroenterology 80:605-614; 1981.
32. Wong, S. H.; Ogle, C. W.; Cho, C. H. The influence of chronic or acute nicotine pretreatment on ethanol-induced gastric ulceration in the rat. J. Pharm. Pharmacol. 38:537-540; 1986.