Caffeine-Induced Gastric Secretion in Rats (37731)

K. KOWALEWSKI

Surgical–Medical Research Institute and Department of Surgery, The University of Alberta, Edmonton, Canada

Caffeine stimulates the secretion of HCl and pepsin in man and cat (1–4) but not in the dog (1, 5). Caffeine is also a known agent inducing peptic ulcers in the cat (1, 5, 6). Post-caffeine gastric secretion in laboratory rats has not been reported to our knowledge. The purpose of the present study was to assess the gastric secretory action of caffeine in rats and compare it with posthistamine and postpentagastrin gastric secretion in these rodents. Rats bearing permanent gastric and vascular cannulas, vagotomized or not, were infused intravenously with caffeine, histamine, and pentagastrin, individually or combined. Gastric secretion collected during the 24-hr stimulation period was analyzed for HCl and pepsin.

Materials and Methods. Male Wistar rats with body weight ranging from 280 to 320 g were used. All surgical procedures were performed under Diabutal anesthesia (44 mg/kg body weight). In some rats, vagotomy of the stomach was carried out on both nerve trunks, using Lambert's technique (7). A chronic gastric fistula was produced in each rat, and a miniature stainless steel cannula was implanted in the anterior wall of the forestomach. At the same operation, a polyethylene tube was implanted in the vena cava. The method of gastric and vascular cannulation was described previously (8). Gastric secretion in rats was studied 2 weeks after surgery, following a 24-hr fasting period. Placed in Bollman cages (9), the animals were infused intravenously with normal saline alone or with drugs dissolved in saline. Infusion of drugs and the simultaneous collection of gastric secretion lasted for 24 hr. The methods of stimulation and juice collection were previously reported (8, 10, 11). The infusion rate of normal saline was 120 ml/kg body weight for 24 hr (12). Maximal stimulation of HCl output in rats, in our laboratory, can be achieved with histamine dihydrochloride, infused in a dose of 100 mg/kg body weight for 24 hr (10), or with pentagastrin, infused in a dose of 7.68 μg/kg body weight for 24 hr (11). These doses were used in the present experiment. Caffeine sodium benzoate was infused in doses of 30, 60, and 120 mg/kg body weight for 24 hr. Distribution of animals according to treatment and/or surgery methods is given in the tables. Gastric juice hydrochloric acid was determined radiometrically (to pH 7) (9, 10) and pepsin by the hemoglobin method (13). The results were evaluated by the Student's t test.

Results. It can be seen in Table I that caffeine, in the three doses used, induced increased output of gastric juice, HCl, and pepsin without affecting the concentration of acid and pepsin. Differences between caffeine-infused and saline-infused rats were significant in respect to outputs. From the three doses used, 60 mg/kg body weight/24 hr was found to be the "maximal dose" as it induced maximal output of juice, HCl, and pepsin in the unit of time studied. It may be noted from Table II that vagotomy resulted in the abolition of HCl in fasting saline-infused rats. In vagotomized rats, the response to caffeine was very significantly reduced: both concentration and output of HCl were many-fold smaller than those in nonstimulated saline-infused intact rats. The effect of caffeine on gastric secretion was compared with the effect of histamine and pentagastrin infused separately or combined, and the results are shown in Table III. The most striking difference between the caffeine group (Table III) and the other groups of rats is

TABLE I. Effect of Intravenous Infusion of Various Doses of Caffeine Sodium Benzoate on Gastric Secretion of Rats Bearing Permanent Gastric Fistulas.[a]

Group	Infusion	Concentration		24-hr output		
		HCl (mEq/liter)	Pepsin (mg/ml)	Volume (ml)	HCl (mEq)	Pepsin (mg)
1	Saline	67 ± 11[b]	20 ± 7	9.7 ± 1.3	0.64 ± 0.1	190 ± 15
2	Caffeine, 30 mg	63 ± 10	22 ± 2	18.5 ± 3.4	1.18 ± 0.3	406 ± 99
3	Caffeine, 60 mg	67 ± 11	25 ± 4	26.0 ± 7.4	1.83 ± 0.7	644 ± 165
4	Caffeine, 120 mg	56 ± 9	21 ± 2	24.0 ± 4.9	1.31 ± 0.3	496 ± 85
p						
Group 1 vs groups 3–5		NS[c]	NS	<0.01	<0.01	<0.01
Group 3 vs groups 2 and 4		NS	NS	<0.05	<0.05	<0.05

[a] Caffeine dissolved in normal saline and administered in 30, 60, and 120 mg/kg body weight/24 hr. Control rats received saline alone. Ten rats in each group.

[b] Average and standard deviation.

[c] NS (not significant) = $p > 0.05$.

the significantly higher concentration and output of HCl in animals treated with histamine and pentagastrin than in animals given caffeine. No summation or potentiation of secretory action was observed when caffeine was infused together with histamine or pentagastrin. The highest output of pepsin was found in pentagastrin-infused rats and the lowest in animals treated with histamine alone or with histamine combined with caffeine. The significance of the differences between the groups is given in Table III.

Discussion. Caffeine stimulates gastric secretion in man and cat but not in the dog (1, 5). As shown by our present study, caffeine also stimulates gastric secretion in the rat. The rat differs, however, in some respects from man and cat regarding its secretory reaction to caffeine. Firstly, caffeine and histamine act synergistically in man and cat in respect to secretion of HCl (2) and pepsin (4). However, such potentiation effect was not observed in rats treated with caffeine and histamine. Secondly, the presence of a summation or potentiation effect on HCl secretion between caffeine and pentagastrin has been observed in man (17) but not in the rat. Finally, there is a difference between the rat and other species regarding the role of the vagus nerve on both spontaneous and

TABLE II. Effect of Intravenous Infusion of Caffeine Sodium Benzoate, 60 mg/kg Body Weight for 24 hr, on Gastric Secretion in Normal and Vagotomized Rats Bearing Permanent Gastric Fistulas.[a]

Group	Infusion	Vagotomy	Concentration		24-hr output		
			HCl (mEq/liter)	Pepsin (mg/ml)	Volume (ml)	HCl (mEq)	Pepsin (mg)
1	Saline	—	67 ± 11[b]	20 ± 7	9.7 ± 1.3	0.64 ± 0.1	190 ± 65
2	Caffeine	—	69 ± 13	25 ± 4	26.0 ± 7.4	1.83 ± 0.7	644 ± 165
3	Saline	+	0	2 ± 1	5.4 ± 1.0	0	9 ± 3
4	Caffeine	+	4.0 ± 3.7	3 ± 1	6.2 ± 1.0	0.02 ± 0.01	10 ± 6
p							
Group 4 vs groups 1 and 2			<0.01	<0.01	<0.01	<0.01	<0.01

[a] Ten rats in each group.

[b] Average and standard deviation.

TABLE III. Comparison of the Secretory Action of Caffeine Sodium Benzoate, Histamine, and Pentagastrin Infused Intravenously, Separately or Combined, on Gastric HCl and Pepsin in Rats.[a]

Group	Infusion	Concentration		24-hr output		
		HCl (mEq/liter)	Pepsin (mg/ml)	Volume (ml)	HCl (mEq)	Pepsin (mg)
1	Caffeine	69 ± 13[b]	25 ± 4	26.0 ± 7.4	1.83 ± 0.7	644 ± 165
2	Histamine	116 ± 14	24 ± 3	23.0 ± 2.8	2.82 ± 0.5	525 ± 121
3	Pentagastrin	135 ± 14	24 ± 2	35.0 ± 4.2	4.87 ± 0.8	840 ± 101
4	Caffeine + histamine	102 ± 28	20 ± 4	28.0 ± 7.0	3.10 ± 1.2	568 ± 190
5	Caffeine + pentagastrin	108 ± 2.5	20 ± 4	34.0 ± 10.0	3.82 ± 1.8	692 ± 226
p						
Group 1 vs groups 2–5		<0.01	—	—	<0.01	—
Group 3 vs groups 1, 2, 4		<0.01	—	<0.01	<0.05	<0.01
Group 4 and 5 vs groups 1–3		—	<0.05	—	—	—

[a] Ten rats in each group.

[b] Average and standard deviation.

caffeine-induced gastric secretion. In the rat, interdigestive spontaneous gastric secretion of HCl is vagus-dependent and represents a true cephalic phase (14, 15). It is totally suppressed by bilateral truncal vagotomy (14, 16). In the rat, such vagotomy had a marked inhibitory effect on caffeine-induced secretion; in fact, only a very small amount of HCl was produced by vagotomized caffeine-treated animals as compared with intact controls. Bilateral vagotomy in the cat, or atropine injection in man and cat, resulted only in a slight reduction of caffeine-induced gastric secretion (3). It was therefore suggested (3) that in man and cat, caffeine acts peripherally on the gastric glandular mechanisms. It results from this study that in the rat most caffeine action on parietal cells is mediated by the vagus nerve. If caffeine has any direct action on the gastric gland cells, such action appears negligible, according to the present experiment.

Summary. The purpose of this study was to assess the action of caffeine as a gastric secretagogue in rats, and to compare it with histamine- or pentagastrin-induced secretion. Rats bearing permanent cannulas of the stomach and the vena cava were infused for 24 hr with normal saline alone (control animals) or with caffeine sodium benzoate, histamine, and pentagastrin, in saline, separately or combined. In doses of 30, 60, and 120 μg/kg body weight for 24 hr, caffeine stimulated output of gastric juice, HCl, and pepsin without significantly affecting the concentration of these components. In this respect, caffeine differed from histamine and pentagastrin, known stimulants of parietal and chief cells in rats. Caffeine did not potentiate the secretory action of histamine or pentagastrin on HCl and pepsin. Following bilateral vagotomy, caffeine-induced gastric secretion was markedly decreased.

The technical assistance of Mrs. T. Hoogen, Mrs. M. McCubbin, and Mr. T. Pachkowski is gratefully acknowledged.

1. Roth, J. A., and Ivy, A. C., Amer. J. Physiol. 141, 454 (1944).

2. Roth, J. A., and Ivy, A. C., Amer. J. Physiol. 142, 107 (1944).

3. Roth, J. A., and Ivy, A. C., Gastroenterology 5, 129 (1945).

4. Grossman, M. I., Roth, J. A., and Ivy, A. C., Gastroenterology 4, 251 (1945).

5. Roth, J. L. A., and Valdes-Dapena, A., *in* "Pathophysiology of Peptic Ulcer" (S. C. Skoryna, ed.), p. 273, McGill University Press, Montreal (1963).

6. Lee, Y. H., and Bianchi, R. G., *in* "Peptic Ulcer" (C. J. Pfeiffer, ed.), p. 329, Munksgaard, Copenhagen (1971).

7. Lambert, R., "Surgery of the Digestive System in the Rat," Thomas, Springfield (1965).

8. Kowalewski, K., and Chmura, G., Arch. Int.

Physiol. Biochim. **77**, 10 (1969).

9. Bollman, J. L., J. Lab. Clin. Med. **33**, 1348 (1948).

10. Kowalewski, K., and Chmura, G., Amer. J. Digest. Dis. **13**, 753 (1968).

11. Kowalewski, K., Arch. Int. Physiol. Biochim. **79**, 545 (1971).

12. Kowalewski, K., Proc. Soc. Exp. Biol. Med. **142**, 586 (1973).

13. Aitken, M. A., Spray, G. H., and Walters, G., Clin. Sci. **13**, 119 (1954).

14. Shay, H., Komarov, S. A., and Gruenstein, M., Arch. Surg. **59**, 210 (1949).

15. Lin, T. M., and Alphin, R. S., A.M.A. Arch. Surg. **192**, 23 (1949).

16. Kowalewski, K., Amer. J. Digest. Dis. **16**, 19 (1971).

17. Cohen, M. M., Debas, H. T., Holubitsky, I. B., and Harrison, R. C., Gastroenterology **61**, 440 (1971).

Received June 24, 1973. P.S.E.B.M., 1973, Vol. 144.