The Effect of Hog Gastrin on Gastric Secretion in Chronic Gastric Fistula Rats

Gastrin has been shown to stimulate gastric secretion in man[1-4], and cats and dogs[5-8], but the rat has rarely been studied[9,10]. This investigation was done to determine the effect of hog gastrin on gastric secretory volume, acidity and peptic activity over a 6 h period in chronic gastric fistula rats.

Male Sprague-Dawley rats from the Charles River Laboratories breeding shed 1 weighing between 200–250 g at the time of cannulation were used. A chronic gastric fistula was prepared according to the method of LANE et al.[11] and the rats were allowed to recover for 10–15 days before study. Not more than 1 experiment/week was done on any animal to allow adequate recovery.

Twenty-four hours prior to experimentation the rats were isolated from food only in a large monkey cage with 1 inch square floor mesh to minimize coprophagy. On the morning of the study the rats were weighed and placed in a semi-circular plexiglas cage (length 23.5 cm, height 6.0 cm, width 6.5 cm and diameter 7.5 cm) and the cannula plug removed. The stomach was repeatedly washed with warm double distilled water until clear. Gastric juice was collected hourly. The first sample was discarded, and the second taken as control. Subsequently 6 experimental collections were made.

Following the control collection, hog gastrin was injected s.c. in the back of the neck. The hypodermic needle was left in place for the subsequent replacement of fluid loss. Fluid loss was replaced by the injection every 2 h of an equivalent volume of normal saline to that of gastric secretion produced in the preceding 2 h. The rats received either 1 or 2 ml hog gastrin. Gastrin was prepared by the method of GILLESPIE and GROSSMAN[12] and doses are expressed as g of hog mucosa from which the extract was derived: 1 ml being equivalent to 10 g mucosa.

The samples were collected on ice and after centrifugation refrigerated until analyzed. Acidity was determined by titrating against 0.1 N NaOH in a microburette using phenolphthalein as indicator. Pepsin was measured by HUNT's method[13]. Gastric volume and acidity were calculated per 100 g rat body weight[14,15]. Data are presented as mean values $\pm$ 1 S.E. P values were determined by the t test.

The effect of gastrin on gastric juice volume and volume per 100 g is indicated in Figure 1. Peak volume secretion was apparent at 1 h with both doses of gastrin ($P < 0.001$) the volume with 1 ml (3.3 ml) being higher than that occurring with 2 ml (3.0 ml). This difference was not significant ($P < 0.50$). Control levels were reached by 4 h after an exponential fall. Acidity, total acidity and acid output are represented in Figure 2. Peak gastric acidity following both doses of gastrin occurred at the third h ($P < 0.001$) and return to the control levels was apparent by the sixth h. Peak total acidity ($P < 0.001$) and acid output ($P < 0.001$) were reached 1 h after the 2 gastrin doses and had returned to control levels by the fourth h.

The effect of gastrin on the concentration and output of pepsin is indicated in Figure 3.

With the 2 doses of gastrin an abrupt fall in the pepsin concentration occurs over the first 2 h ($P < 0.01$) followed by a rise reaching a peak at the 6th h ($P < 0.1$). Pepsin output (total pepsin) initially rises within the first h ($P < 0.001$) and has returned to control levels by the third–fourth h. A further increase is seen by the sixth h ($P < 0.05$).

This report indicates that hog gastrin is a potent stimulant of gastric secretion in the chronic gastric fistula rat. Gastric juice volume, total acidity and acid output show a peak response at 1 h, whereas acidity reaches its maximum by the third h. Pepsin stimulation is delayed until the sixth h and is not strong. ADASHEK and GROSSMAN[9] found that in gastric fistula rats, peak acid output increased within the first h with increasing doses of hog gastrin (1.25–10.0 g). SCHOENFIELD et al.[10] have reported similar data for volume and acid output to that indicated here, but state that pepsin is unaffected by gastrin. These authors, however, only studied animals over a 4 h period.

The fall in pepsin concentration (Figure 3) over the first 2 h ($P < 0.01$) reflects dilution by the increased volume of parietal cell secretion. The initial increase in

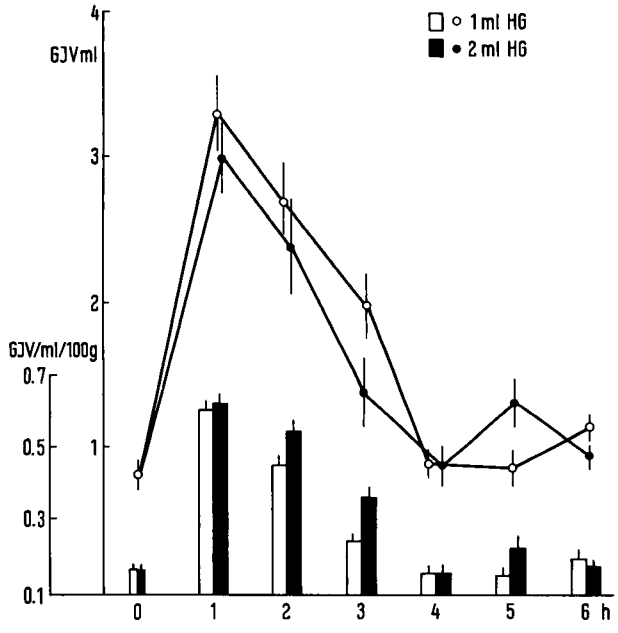

Fig. 1. Gastric juice volume and gastric juice volume/100 g following 1 or 2 ml hog gastrin. Each point represents the mean value $\pm$ 1 S.E. for experiments on 2–14 rats.

[1] G. M. MAKHLOUF, J. P. A. MCMANUS and W. I. CARD, Gut *5*, 379 (1964).
[2] G. M. MAKHLOUF, J. P. A. MCMANUS and W. I. CARD, Lancet *2*, 485 (1964).
[3] G. M. MAKHLOUF, J. P. A. MCMANUS and W. I. CARD, Gut *6*, 525 (1965).
[4] L. S. SEMB and J. A. MYREN, Scand. J. clin. Lab. Invest. *17*, 311 (1965).
[5] S. EMÅS and B. FYRÖ, Acta physiol. scand. *63*, 358 (1965).
[6] I. E. GILLESPIE and M. I. GROSSMAN, Am. J. Physiol. *203*, 557 (1962).
[7] S. KONTUREK and M. I. GROSSMAN, Gastroenterology *50*, 650 (1966).
[8] A. R. COOKE, D. L. NAHRWOLD, R. M. PRESHAW and M. I. GROSSMAN, Am. J. Physiol. *213*, 432 (1967).
[9] K. ADASHEK and M. I. GROSSMAN, Proc. Soc. exp. Biol. Med. *111*, 629 (1963).
[10] L. J. SCHOENFIELD, H. SIPLET and S. A. KOMAROV, Am. J. dig. Dis. *11*, 113 (1966).
[11] A. LANE, A. C. IVY and E. K. IVY, Am. J. Physiol. *190*, 221 (1957).
[12] I. E. GILLESPIE and M. I. GROSSMAN, Gastroenterology *44*, 301 (1963).
[13] J. N. HUNT, Biochem. J. *42*, 104 (1948).
[14] R. J. MADDEN, H. H. RAMSBURG and J. M. HUNDLEY, Gastroenterology *18*, 119 (1951).
[15] S. P. BRALOW and S. A. KOMAROV, Am. J. Physiol. *203*, 550 (1962).

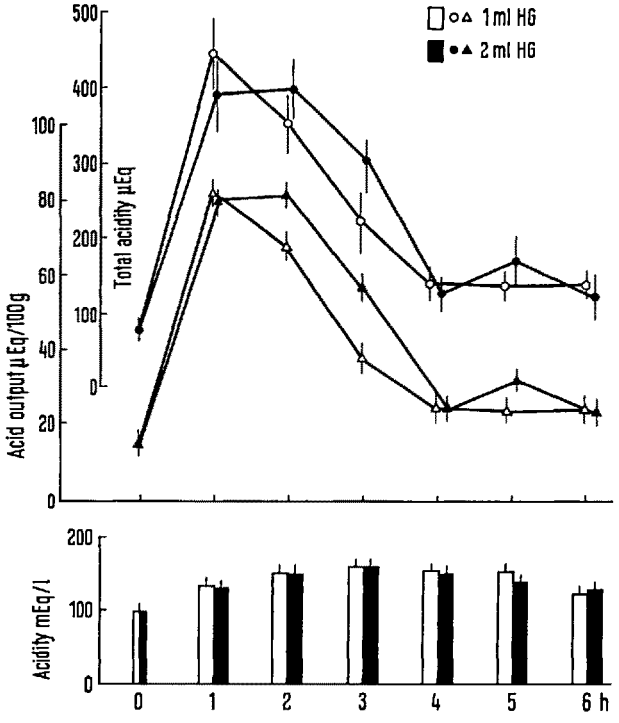

Fig. 2. Acidity, total acidity and acid output following 1 or 2 ml hog gastrin. Each point represents the mean value ± 1 S.E. for experiments on 2–14 rats.

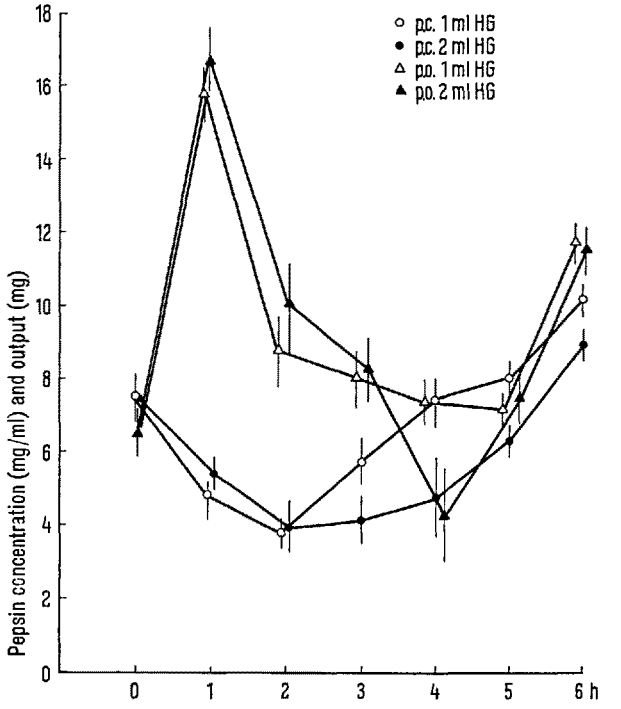

Fig. 3. Pepsin concentration (p.c.) and pepsin output (p.o.) following 1 or 2 ml hog gastrin. Each point represents the mean value ± 1 S.E. for experiments on 2–14 rats.

Comparison of hog gastrin and ICI 50123 in stimulating gastric secretion

Parameter	Hog gastrin			ICI 50123
	10 g	20 g	$^1/_{20}$ mg[a] $^1/_{80}$ mg[a] 10 g[b]	40 g/100 g[c]
First hour				
Volume	3.3 ± 0.3	3.0 ± 0.3	2.8	3.8 ± 0.4
Volume/100 g	0.612 ± 0.05	0.624 ± 0.06		0.694 ± 0.028
Acidity	132 ± 4	129 ± 3		131 ± 6
Total acidity	446.7 ± 45.7	386.6 ± 29.6	400 500	484 ± 37.0
Acid output	0.0833 ± 0.01295	0.0800 ± 0.0065		0.0894 ± 0.010
Pepsin	4.8 ± 0.40	5.4 ± 0.5		3.9 ± 0.5
Total pepsin	15.8 ± 1.5	16.8 ± 2.7		15.6 ± 4.1
Second hour				
Volume	2.4 ± 0.3	2.7 ± 0.3	1.0	1.8 ± 0.2
Volume/100 g	0.454 ± 0.065	0.549 ± 0.056		0.311 ± 0.046
Acidity	149 ± 3	149 ± 2		141 ± 5
Total acidity	354.7 ± 46.2	402.0 ± 50.4	250	243.6 ± 38.3
Acid output	0.0681 ± 0.0109	0.0825 ± 0.0090		0.0439 ± 0.006
Pepsin	3.8 ± 0.2	3.9 ± 0.5		2.8 ± 0.6
Total pepsin	8.8 ± 1.0	10.1 ± 1.4		4.7 ± 1.0

[a] Reference [10], [b] reference [9], [c] reference [16].

the pepsin output ($P < 0.001$) reflects a 'washing out' phenomenon. However, the low levels in pepsin output between the second and fourth h at a time when gastric juice volume is high may reflect a true suppression of pepsin secretion, particularly with the higher dose of gastrin in the fourth hourly collection. Of more importance is the stimulation of pepsin output commencing between the fifth and sixth h. This is only a weak stimulation and may be found to be greater with longer time periods of collection. The reason why stimulation of pepsin output is delayed to the fifth–sixth h is unknown.

It is difficult to relate the potency of hog gastrin to that of the synthetic gastrin ICI 50123 (Ayerst Labora-

[16] Y. H. LEE and J. H. THOMPSON, in preparation.

tories Inc., New York). However, by comparing data obtained under maximal stimulation with both agents (Table) essentially similar results are obtained. It is of interest that the effect produced by hog gastrin persists longer than that induced by ICI 50123[17,18].

Résumé. L'action de la gastrine de porc a été étudiée chez des rats mâles munis de fistules gastriques. La gastrine était injectée par voie s.c. à des doses de 1–2 ml: 1 ml équivalant à l'activité de 10 g de muqueuse de porc. Le volume de suc gastrique, le volume de suc gastrique par 100 g, l'acidité totale et le débit d'acide accusèrent une pointe dans la première h, alors que la concentration en acide atteignit son maximum vers la troisième h. Le débit de la pepsine diminua entre la troisième et la cinquième h et augmenta légèrement entre la cinquième et la sixième h.

Y. H. Lee and J. H. Thompson

Department of Pharmacology and Experimental Therapeutics, UCLA School of Medicine, Los Angeles (California 90024, USA), 19 January 1968.

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Responses of Oculomotor Nucleus and Marginal Gyrus in Sleep

The role of several brainstem structures in the production of sleep characteristics has been under investigation in recent years employing mainly the lesion techniques. Because of the difficulties in recording with free-moving animals, there have not been many electrophysiological investigations on the particular areas. Evoked potential techniques have been used more commonly with the limitations implied. More reliability is possible if the degree of change of successive responses rather than the absolute values of amplitudes of potentials is considered. This method has been adapted here.

Rapid eye movements of sleep (REMS) occurring in the desynchronized state of sleep can be abolished by lesions of either the vestibular nuclei[1] or the superior colliculi[2]. It is not known whether the 2 structures play similar or distinct roles under influences of pontine reticular areas[3]. This is a report on the nature of recovery of responsiveness of oculomotor nucleus to stimulations of nucleus reticularis pontis oralis (RPO), medial vestibular nucleus (MVN) and superior colliculus (SCO) during sleep and wakefulness. The responsiveness of visual cortex (marginal gyrus) has also been simultaneously studied as lesions of the same were also shown to impair REMS[2]. The recovery was measured by calculating the ratio of amplitudes of potentials (late components), second (R2) to first (R1) in a pair evoked by a pair of stimuli[4]. Nineteen experiments were done on free-moving cats carrying electrodes implanted chronically for recording surface and depth electroencephalogram, electrooculogram and electromyogram, and for delivering stimuli as described before[5,6]. Recordings were made on a setup including a Grass 8 channel electroencephalograph, two Grass S-4 stimulators with isolation units coupled together and a Dumont oscilloscope. Stimulus intensity ranged from 1–6 V, set at a level that could evoke clear potentials without causing apparent changes in the on-going EEG or in the behaviour of the cat. Stimuli of a pair were of identical amplitude and of 0.3 msec duration, delivered in pairs with an inter-pulse interval of about 100 msec. The paired stimuli of set parameters were delivered at intervals throughout sleep-wakefulness cycles.

Responsiveness of oculomotor nucleus to stimulations of medial vestibular nucleus showed a characteristic decrease in sleep compared to wakefulness (Figure 1). Similar decrease of responsiveness was observed in the cortex also (Figure 2). It has, however, to be noted that the amplitudes of single potentials (R1) increased in sleep; only the succeeding responses (R2) decreased (Table). This suggests that following each response there is a prolonged inhibition. It was noted earlier[7] that discharges of vestibular nucleus produce brief bursts of activity followed by prolonged periods of silence in oculomotor nucleus. It was also reported that vestibular neurons discharge in bursts during REMS[8].

Responsiveness of oculomotor nucleus to collicular stimulations was not different in sleep from wakefulness

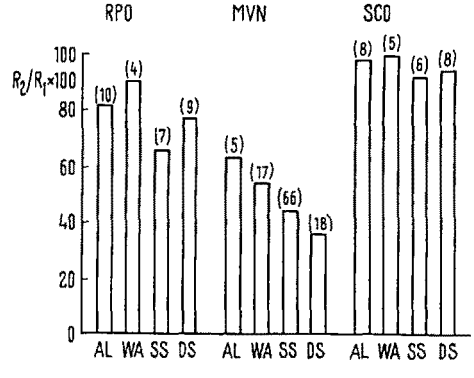

Fig. 1. Recovery of responsiveness of oculomotor nucleus to influences of RPO, MVN, and SCO during sleep and wakefulness. For abbreviations see the Table. Values in parenthesis indicate the number of pairs of responses averaged.

[1] O. Pompeiano and A. R. Morrison, Experientia *22*, 60 (1965).

[2] M. Jeannerod, J. Mouret and M. Jouvet, Electroenceph. clin. Neurophysiol. *18*, 554 (1965).

[3] M. Jouvet, Physiol. Rev. *47*, 117 (1967).

[4] M. Palestini, M. Pisano, G. Rosadini and G. F. Rossi, Electroenceph. clin. Neurophysiol. *19*, 276 (1965).

[5] T. Desiraju, B. K. Anand and B. Singh, Physiol. Behav. *1*, 285 (1966).

[6] T. Desiraju, B. K. Anand and B. Singh, Physiol. Behav. *2*, 185 (1967).

[7] E. Manni, G. B. Azzena, H. Casey and R. S. Dow, Expl Neurol. *12*, 9 (1965).

[8] E. Bizzi, O. Pompeiano and I. Somogyi, Archs ital. Biol. *102*, 308 (1964).