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Studies on a Mechanism of Enhancement of Maximum Gastric Secretory Response: Its Possible Importance in Recurrent Ulcers after Surgical Treatment

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The determination of maximum gastric secretory response to histamine, histalog and pentagastrin is considered as the clinically most important test of gastric secretion. In man and dogs, Marks *et al.* [1, 2] examined whether there exists a relationship between the maximum secretory response to histamine and the parietal cell mass of the stomach and found a highly significant correlation between these two parameters. However, in a simplified interpretation of these results [3], the maximum gastric secretory response to various stimuli was set equal to the secretory capacity of the stomach, within small limits. However, in our *in vivo* studies with amodiaquine, a strong inhibitor of gastric histamine methyltransferase *in vitro*, we obtained results which are incompatible with such an hypothesis.

Methods. In 8 mongrel dogs (both sexes, 14—30 kg) with Heidenhain pouches secretory tests were carried out not prior than 6 weeks after operation, in the same room, at the same time of day and the same day of the week twice a week during 10 months. First, the maximum secretory responses of the pouches to i.m. administered pentagastrin (Merck, Darmstadt) and histamine were determined by dose-response curves and were considered to be reproducible when at least 3 consecutive stimulations with maximum doses of both substances induced the same volumes of

Table 1. *Enhancement of maximum gastric secretory response to pentagastrin and histamine by amodiaquine*

Amodiaquine [mg/kg]	Enhancement in per cent					
	Pentagastrin [6 μg/kg]			Histamine [40 μg/kg]		
	n	volume	acid output	*n*	volume	acid output
0.25	3	0	0	1	0	0
0.5	5	16 ± 10	21 ± 8	1	0	0
1.0	11	25 ± 7	40 ± 6	3	30 ± 9	31 ± 19
2.0	13	48 ± 8	62 ± 5	4	33 ± 21	73 ± 36
3.0	7	22 ± 11	42 ± 10	3	21 ± 14	18 ± 12

$\bar{x} \pm$ S.D., n = number of experiments.

gastric juice and acid outputs within a limit of ±5%. Then a test with pentagastrin or histamine alone was followed by one with pentagastrin or histamine plus amodiaquine (Parke & Davis Comp., Munich) and a second one with pentagastrin or histamine alone. Amodiaquine was administered i.m. 30 min before the stimulant. Gastric juice was collected in half-hour portions during 2 hrs. The acid output was determined by titration with 0.1 N NaOH (Titrisol, Merck) up to pH 7.0 using the glass electrode, and the gastric acid secretion was defined as the peak hour response to pentagastrin or histamine. Sufficient denervation of the pouches was shown by a standard insulin test 4—6 months after operation.

Results. Maximum secretory response to pentagastrin and histamine in dogs was obtained with 6 and 40 μg/kg. On the average, 20 ml/hr of gastric juice and 2.4 mval/hr of acid output were secreted after pentagastrin, and twice as much after histamine.

As Table 1 shows, maximum gastric secretion stimulated by pentagastrin and histamine is augmented by pretreatment of the dogs with several doses of amodiaquine, the optimum being 2 mg/kg.

Salivary secretion from submandibular and parotid glands in dogs induced by 40 μg/kg pilocarpine (i.a. into the maxillary artery) was affected by amodiaquine in a different manner: From 15 dogs, only 1 dog showed in 4 experiments an increase of salivation, 6 showed an inhibition of maximum 50% and 8 revealed no effects of amodiaquine on salivation even after injection of 4 mg/kg of the drug. Furthermore, in 6 dogs no effect of amodiaquine on pancreatic and biliary secretion induced by secretin (Boots Pure Drug, Nottingham, 1 U/kg i.a. into the a. pancreaticoduodenalis) could be observed.

Discussion. The enhancement of the maximum gastric secretory response to pentagastrin and histamine by amodiaquine may be considered as a further argument for the hypothesis that histamine is a physiological stimulator of gastric secretion. Amodiaquine did not act as a stabil choline ester since it showed no direct action on gastric secretion. Furthermore, the enhancement of the maximum secretory response is incompatible with the idea, that this response may reflect the secretory capacity

of the stomach. Also Norgard *et al.* [4] found fluctuations of the maximum histalog response in man of about 200%, which cannot be explained by short-lastening variations of the parietal cell mass. A functional parietal cell mass was assumed which may be smaller than the histochemically determined parietal cell mass.

A similar effect as seen after amodiaquine should be observed with natural inhibitors of histamine methyltransferase, i.e. with methylhistamine, or in patients who show a deficit of this enzyme in the gastric mucosa. Both these mechanisms may not be influenced by vagotomy or resection, as our results on a denervated part of the stomach show, and may be therefore in some cases responsible for recurrent ulcers even after complete vagotomy.

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Untersuchungen zur Entstehung der Streß-Ulcera

Investigations on the Formation of Stress Ulcers

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Zwei physiologische Funktionen können dem Histamin zugeschrieben werden:

1. eine Regulierung der Mikrozirkulation,
2. eine Stimulierung der Magensaft- und Speichelsekretion.