Pharmacological evidence is compatible with the suggestion that decreased central NA release is associated with REM sleep. In cats, inhibition of NA synthesis[51-53] or specific lesions of NA pathways[54] increase REM sleep time. In rats, the same results have been reported[55,56], whereas intraventricular administration of NA itself decreases REM sleep time[57].

We do not know how central NA exerts its widespread effects on neuronal firing rates and CBF. However, it is known that increases of regional CBF do occur during increased cerebral functional activity[58-62]. Likewise, increases of regional brain oxidative metabolism occur during increased brain functional activity[30,63-67], and it is believed that the activity-related increases of CBF serve to meet the increased energy demand incurred by elevated brain functional activity. It is possible, therefore, that observed noradrenergic effects on CBF are only secondary to the alterations of neuronal activity caused by a primary noradrenergic modulation of firing rates. If this were so, NA would act as presumably many neurotransmitters do, except that it would do so throughout the brain.

An alternative possibility is that central NA exerts primary control over CBF, neuronal firing rates, and perhaps even over oxidative metabolism. Brain is dependent on the continuous provision of both glucose and oxygen for oxidative metabolism[68], and it cannot sustain itself by anaerobic glycolysis[68] or by mobilization of glycogen stores[69-70]. A primary noradrenergic control of brain glucose consumption and CBF colud serve as a safety factor to increase oxidative metabolism quickly, protecting the brain from an energy debt for the first few moments after sudden changes in functional activity[71]. If this possibility were true, central NA might be an unusual neurotransmitter[72].

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72 Note added in proof: Recently electrical stimulation of the locus coeruleus has also been shown to decrease CBF [J. C. de la Torre, Neuroscience *1*, 455 (1976)].

Influence of metiamide and atropine on pepsinogen secretion in the conscious rat

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Summary. Activity of peptic cells is influenced directly by cholinolytic or cholinergic agents. Histamine H_2-antagonists influence the activity of the chief cells through changes of acidity of gastric juice.

The histamine H_2-antagonists inhibit not only the histamine-induced but also the cholinergic-stimulated gastric acid secretion[2-4]. Whether the H_2-antagonists are also able to influence the pepsinogen secretion remains to be clarified. Konturek et al.[5] found that pepsinogen secretion was inhibited by metiamide, but this effect of metiamide was not shown in the experiments of Gibson et al.[6]. They showed that while metiamide inhibited the pepsinogen secretion stimulated by pentagastrin, the cholinergic-induced pepsinogen secretion could not be diminished and was in fact enhanced.

In our experiments, we wanted to investigate the role of histamine H_2-receptors and cholinergic receptors in pepsinogen secretion.

Method. Chronic gastric fistulae were prepared in pentobarbitone (30 kg mg^{-1} i.p.) anaesthetized male albino rats (SIV 50, Ivanovas, Kisslegg) weighing 200–230 g according to Lane et al.[7]. A postoperative period of 2 weeks was allowed. Before each experiment, the rats were starved for 48 h and kept in individual cages to prevent coprophagia. The collection of gastric juice was carried out in modified Bollman-cages. The stomachs were washed with warm water (ca. 50 ml). The 1st fraction (60 min) of gastric juice was eliminated because the distension of the stomach wall by the wash can falsify the secretory values. After this the gastric secretion was collected each hour. The gastric juice was centrifuged, the volume measured, and the acid content titrated by an autoburette (ABU 12, Radiometer, Copenhagen, Denmark). The pepsin activity was determined by the method of Debnath et al.[8] using hemoglobin as substrate and expressed in μmoles splitted tyrosine/min.

The gastric secretion was stimulated by histamine (as hydrochloride, Fluka AG, Buchs, Switzerland), pentagastrin (Gastrodiagnost, Merck AG, Darmstadt) and carbachol (Doryl, Merck AG, Darmstadt) infused into the tail vein in stepwise increasing dosis. Metiamide (Smith, Kline and French Labs Ltd, Welwyn Garden City,

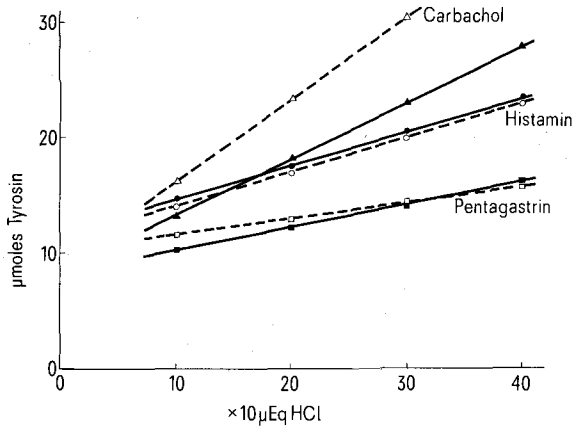

Fig. 1. The effect of metiamide (1 µmole 100 g^{-1} h^{-1}) on gastric secretion stimulated by different secretagogs. Unbroken lines represent the correlation between acid and pepsinogen at stimulated secretion, broken lines are the correlation-lines of stimulated secretion in presence of metiamide. Equations: for pentagastrin: y = 0.20 x + 8.1 (r = 0.4659, n = 24), for pentagastrin + metiamide: y = 0.14 x + 10 (r = 0.3398, n = 44), for histamine: y = 0.29 x + 11.5 (r = 0.3368, n = 120), for histamine + metiamide: y = 0.30 x + 11.1 (r = 0.4785, n = 48), for carbachol: y = 0.49 x + 8.3 (r = 0.6288, n = 76), for carbachol + metiamide: y = 0.70 x + 9.1 (r = 0.5479, n = 42).

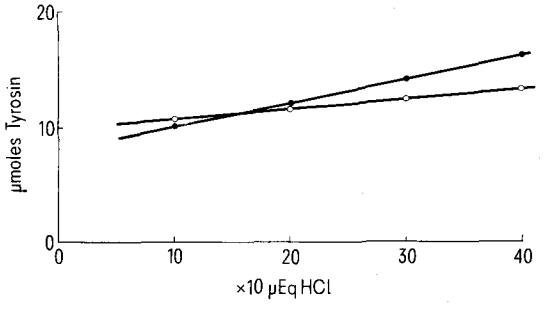

Fig. 2. The effect of atropine on acid and pepsinogen secretion stimulated by pentagastrin. ●—● Pentagastrin (y = 0.22 x + 8.3, r = 0.6675, n = 32); ○—○ pentagastrin + atropine (0.02 µmoles 100 g^{-1} h^{-1}) (y = 0.09 x + 9.8, r = 0.3765, n = 42).

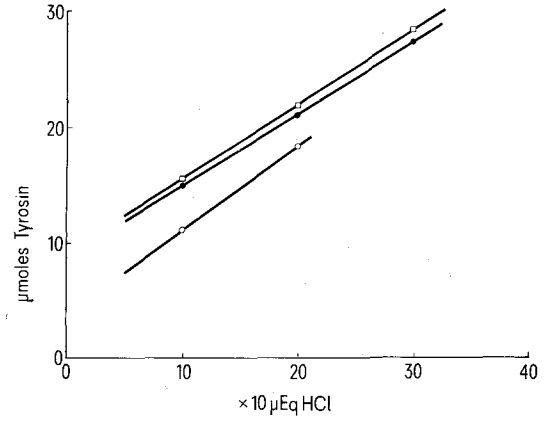

Fig. 3. The effect of atropine on acid and pepsinogen secretion induced by carbachol. ●—● Carbachol (y = 0.62 x + 8.8, r = 0.7258, n = 42); □—□ carbachol + atropine (0.01 µmoles 100 g^{-1} h^{-1}) (y = 0.64 x + 9.3, r = 0.8047, n = 19); ○—○ carbachol + atropine (0.05 µmoles 100 g^{-1} h^{-1}) (y = 0.72 x + 3.9, r = 0.7577, n = 15).

England) and atropine (as sulphate, Merck AG, Darmstadt) were given also in infusion i.p.

Results. The 3 secretagogs used stimulated both H^+ and pepsinogen secretion. However, the relationship between acid and pepsinogen secretion differed among the 3 agents. For a given acid output stimulated by carbachol, the pepsinogen secretion was significantly greater than when stimulated by either histamine or pentagastrin. In the presence of metiamide, this relationship did not change for histamine or pentagastrin, but carbachol stimulation caused a greater pepsinogen secretion at a given acid output (figure 1).

Atropine (0.02 µmoles 100 g^{-1} h^{-1}) slightly decreased the pepsinogen secretion for a given HCl-production in response to stimulation by pentagastrin (figure 2).

In another series of experiments, a low dose of atropine (0.01 µmoles 100 g^{-1} h^{-1}) did not alter the relationship between pepsinogen and acid secretion stimulated by carbachol (figure 3). However, when the atropine-dose was increased to 0.05 µmoles kg^{-1} h^{-1}, the pepsinogen secretion was significantly decreased at a given acid secretion, although the relationship between the 2 parameters was similar to control (figure 3).

Discussion. Although the role of the different receptor systems involved in gastric acid secretion have recently been clarified, the regulation of the pepsinogen secretion is still obscure. Administration of cholinolytics, e.g. atropine brought about a strong inhibition of the stimulated pepsinogen secretion[9]. Gibson et al.[6] suggested that the peptic cells possess at least 2 receptors, 1 for histaminergic (probably H_2) and 1 for cholinergic stimulation. On the basis of our results, we would suggest that the independence of pepsinogen secretion with acid secretion is only partly correct for 2 reasons: a) The peptic cells have a cholinergic receptor. Atropine could more strongly inhibit pepsinogen secretion evoked by pentagastrin than acid production. During the carbachol stimulation, atropine caused a parallel displacement to the right of the pepsinogen-acid-relationship (figures 1 and 2). Presumably the cholinergic receptors of the chief cells are more sensitive to atropine than the receptors located at the parietal cells. b) On the chief cells, we suggest that there are no histaminergic receptors but the inhibition of pepsinogen secretion by H_2-antagonists is a secondary consequence of the decrease in the acid production. The fact that both pepsinogen- and acid-secretion are equally inhibited by metiamide, suggests that the activity of the peptic cells is influenced from the histaminergic site only indirectly by causing changes in the acid secretion.

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