creased glycogen concentration in reserpine-treated animals (Figure 3), but only if it was measured 2 h after chlorimipramine injection (or 24 h after reserpine). 6 h after chlorimipramine (or 28 h after reserpine) glycogen content has found to be increased. In this time, glycogen concentration was nearly doubled compared with the sum of glycogen contents measured in the same time after treatment by reserpine or chlorimipramine. Actually, this could not be ruled out for thalamus since glycogen content was more than twice as high as the simple sum of effects, both of reserpine or chlorimipramine, when were given alone.

Many authors have shown that changes in cyclic AMP level can influence glycogen metabolism in rat brain. BRECKENRIDGE[11] found that increased level of cyclic AMP is followed by greater conversion of phosphorylase *b* to phosphorylase *a* and vice versa; phenobarbital treatment leads to a lowering of the level of cyclic AMP and to a decreased conversion of phosphorylase *b* to phosphorylase *a*. The glycogen concentration was decreased[12] at the time when the activity of phosphorylase *a* and cyclic AMP levels were markedly increased[13,14]. So it seems that glycogen concentration could be taken as indirect evidence for cyclic AMP activity.

On the other hand, changes in metabolism of catecholamines in the CNS may be followed by changes in central glycogen metabolism[12], and many centrally acting, which are able to modulate synthesis, release or breakdown of cerebral catecholamines, may also affect cerebral glycogen content. Results of our experiments have confirmed the finding of these authors that reserpine injection significantly increased glycogen content in CNS of rats. Our previous results showed that repeated injections of reserpine, in the course of 3 days, did not affect the glycogen concentration in rat brain[15]. In contrast to reserpine, chlorimipramine per se produced decrease of glycogen content, when it was measured 2 h after drug treatment. This could be explained by a blocking action of chlorimipramine on uptake of noradrenaline in presynaptic neurons and a consequently induced increase of cyclic AMP response to noradrenaline. Such a hypothesis, however, could not be taken as an explanation of increased glycogen levels which appeared 4 and 6 h after chlorimipramine treatment.

Imipramine has no effect on glycogen content in the brain of the mouse[12]. It also failed to show any effect on cyclic AMP content per se, but is able to counteract noradrenaline induced increase of c-AMP in vitro conditions in rats[3]. The divergence between our results and those above mentioned suggested different modes of chlorimipramine and imipramine action. It also can be explained by the differences in species or different experimental conditions. Combined treatment of rats by reserpine and chlorimipramine suggested an antagonistic action of the latter drug. This antagonism was evident only 2 h after chlorimipramine, i.e. 24 h after reserpine. After that time, antagonism disappeared and glycogen content was nearly doubled in all brain structures of treated animals. It is therefore very difficult to conclude either about antagonistic action of chlorimipramine on reserpine increased glycogen content, or about addative action of these two drugs. Perhaps it is better to conclude a dominant action of chlorimipramine in this particular experimental set up.

Résumé. La rézerpine (1 mg/kg) provoque une augmentation significative du taux de glycogène dans le cerveau du rat, surtout 26 et 28 h après le traitement. Contrairement à la rézerpine, la chlorimipramine (25 mg/kg) a une activité de base: 2 h après le traitement, le contenu du glycogène se réduit sensiblement, mais, 6 h plus tard, il augmente fortement, en comparaison avec les valeurs de contrôle. La chlorimipramine a le même effet dans le cerveau des animaux qui étaient 24 h préalablement traités à la rézerpine.

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Effect of Burimamide and Metiamide on Pentagastrin-Stimulated Gastric Acid Secretion and Gastric Mucosal Blood Flow in Cats

Although coming from the same chemical strain, the two histamine-H_2-receptor-antagonists, burimamide and metiamide, seem to be unequal brothers in some aspects: burimamide is generally regarded as inactive after oral administration, metiamide is well absorbed from the gastrointestinal tract[1]. Burimamide releases catecholamines[2,3], metiamide does not[3]. Burimamide inhibits gastric mucosal histamine methyltransferase; metiamide stimulates the enzyme at low concentrations and inhibits it at high concentrations[4]. The present paper describes the difference between burimamide and metiamide with regard to their inhibitory effects on pentagastrin-stimulated gastric acid secretion and gastric mucosal blood flow.

Methods. The experiments were done on cats (1.5–4.5 kg) of either sex under thiopental (60 mg/kg i.p.) and chloralose (30 mg/kg i.v.) anaesthesia. After a starvation period of 24 h, with free access to drinking water, the animals were provided with an acute gastric fistula from which the gastric juice was drained by gravity and collected in 15-min periods. Acidity of the gastric juice, the volume of which was read to the nearest 0.1 ml, was determined by endpoint titration to pH 7.0 with 0.1 *N* sodium hydroxide (Autoburette Radiometer, Copenhagen). Chloride concentration was determined argentometrically (chloride titrator CMT 10 Radiometer, Copenhagen). After a postoperative recovery period of 30 min, basal gastric secretion was collected for 1 h, after

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which gastric acid secretion was stimulated by 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ pentagastrin[5] i.v. for $4^1/_2$h. Gastric mucosal blood flow was determined by the aminopyrine clearance technique[6], where the load was started 30 min before gastric acid secretion was stimulated. Blood samples were taken from the right femoral artery in 30 min intervals. Burimamide[7] (4 mg/kg) and metiamide[7] (2.9 mg/kg) were injected i.v. 60 or 90 min after the start of infusion.

Results. The secretory response to pentagastrin ($N = 5$) (Figure 1) was characterized by a rapid rise with subsequent fading where the volume reached a maximum of 11 ml/30 min and levelled out to about 5 ml/30 min after 2 h. Acid secretion and gastric mucosal blood flow went roughly parallel with volume secretion. H^+ concentration had the tendency to drop from about 145 mEq/l to about 110 mEq/l. Cl^- concentration remained rather stable at about 170 mEq/l. In none of these parameters did burimamide ($N = 3$) produce a measurable inhibition (Figure 2). Metiamide ($N = 3$) caused a pronounced inhibition of gastric secretion including H^+ concentration and gastric mucosal blood flow (Figure 3). Cl^- concentration remained almost unaffected.

Discussion. The failure of burimamide to reduce pentagastrin-stimulated gastric acid secretion and gastric mucosal blood flow contrasts with other investigations on anaesthetized cats[1,9], although the dose we used was slightly larger than that used by BLACK et al.[8]. REED's[9] preparation is not comparable with ours, since in his experiments 2 mg/kg burimamide were infused over 10 min close arterially to the stomach, so that the local concentration of burimamide might have been well above ours. The stable ratio R (gastric mucosal blood

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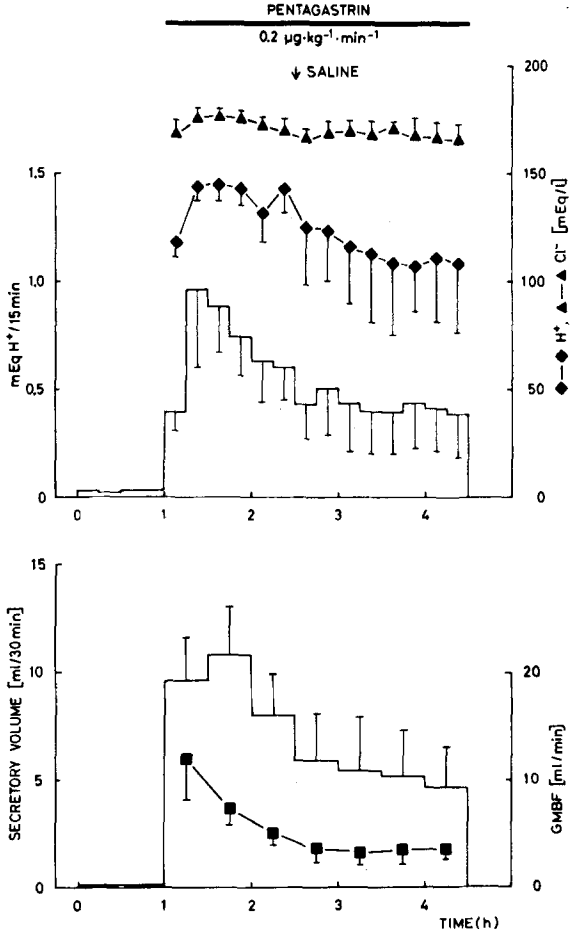


Fig. 1. Gastric secretion of anaesthetized gastric fistula cats in response to 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ pentagastrin i.v. Top: acid output and H^+ and Cl^- concentration, bottom: secretory volume and gastric mucosal blood flow (■). $N = 5$; vertical bars = SEM.

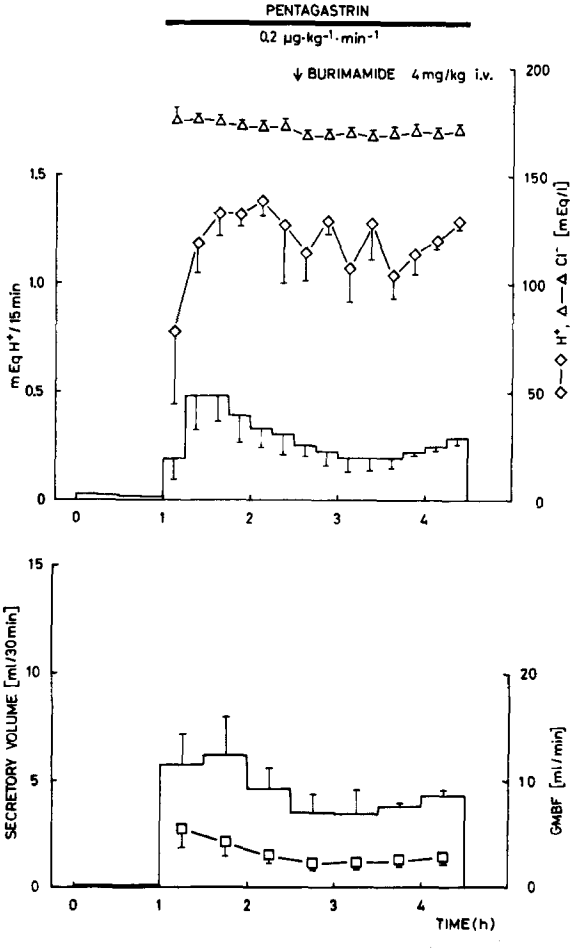


Fig. 2. Effect of 4 mg/kg burimamide on pentagastrin-stimulated gastric secretion and mucosal blood flow in anaesthetized gastric fistula cats. Top: acid output and H^+ and Cl^- concentration, bottom: secretory volume and gastric mucosal blood flow (□). $N = 3$; vertical bars = SEM.

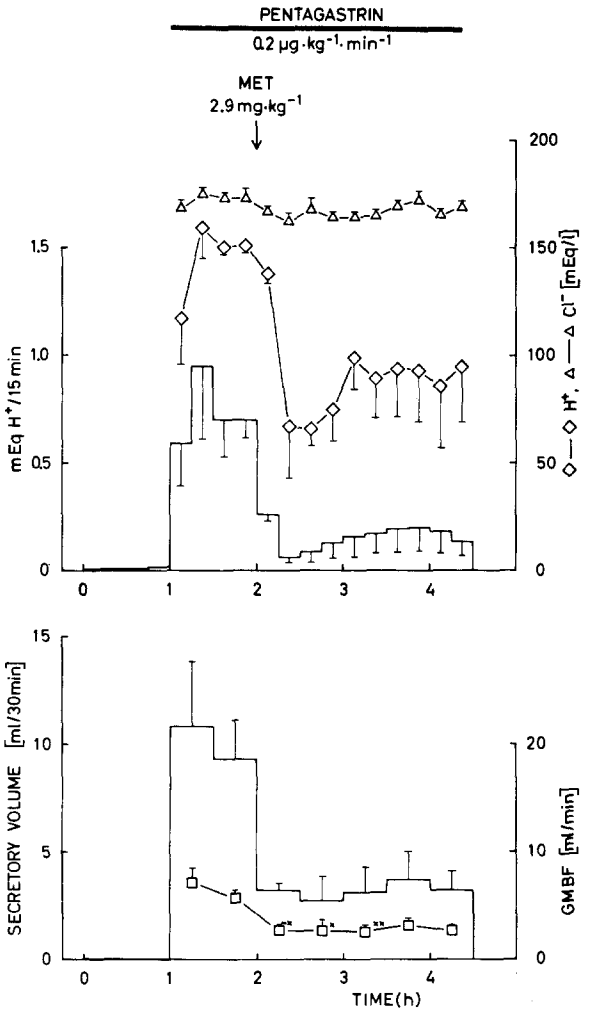
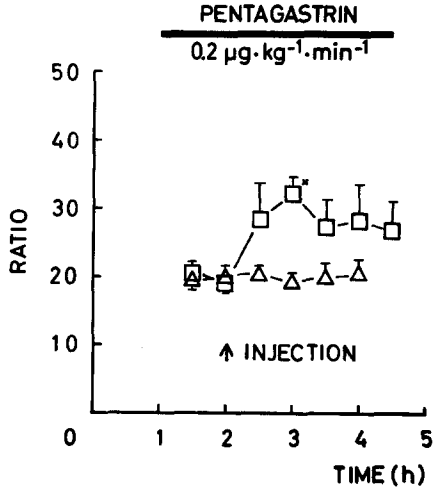


Fig. 3. Effect of 2.9 mg/kg metiamide (MET) on pentagastrin-stimulated gastric secretion and mucosal blood flow in anaesthetized gastric fistula cats. Top: acid output and H^+ and Cl^- concentration, bottom: secretory volume and gastric mucosal blood flow (□). Differences between the last value before and those after metiamide are marked by x when significant at the 5% level, by xx when significant at the 1% level. $N = 3$; vertical bars = SEM.



flow [ml/min]/secretion rate [ml/min]) in our experiments reflects the unchanged secretion rate and gastric mucosal blood flow.

In contrast to burimamide, metiamide produces a sustained inhibition of pentagastrin-stimulated secretion and gastric mucosal blood flow even in a dose lower than that of burimamide. The inhibitory effect of metiamide can be explained by the hypothesis which was put forward by GROSSMAN and KONTUREK[10] that the parietal cell contains one receptor site for histamine, another one for gastrin-like peptides and a third one for cholinergic stimulants. Blockade of one of these receptors modifies the properties of the other two so that they react with reduced sensitivity on the specific stimulant. The concomitant reduction of the pentagastrin-enhanced gastric mucosal blood flow by a histamine-H_2-receptor-antagonist touches the problem of the relationship between gastrin and histamine in the parietal cell area. Although pentagastrin in submaximal doses does not reduce gastric mucosal histamine in rats[11], the local turnover rate of histamine is increased under the influence of pentagastrin[12]. Such a comparison can be made only with reservations since histamine metabolism and localization in cats differ considerably from that in rats. However, pentagastrin significantly elevates histamine concentration in the feline gastric mucosa[13]. From that, one is tempted to speculate that histamine during pentagastrin-stimulated gastric secretion may play a role in regulating gastric mucosal microcirculation. The increased ratio after metiamide (Figure 4) demonstrates that gastric secretion is inhibited to a greater extent than gastric mucosal blood flow, indicating that during pentagastrin-stimulation gastric acid secretion reacts more sensitively to a blockade of histamine-H_2-receptors than gastric mucosal blood flow does.

Zusammenfassung. Bei narkotisierten Katzen mit einer Magenfistel werden die pentagastrin-stimulierte Magensekretion und Magenschleimhautdurchblutung durch den Histamin-H_2-Rezeptor-Antagonisten Metiamid, nicht jedoch durch Burimamid gehemmt. Die Hemmung wird durch das 3-Rezeptoren-Modell von GROSSMAN und KONTUREK[10] erklärt. Histamin mag bei der Stimulierung der Magensekretion durch Pentagastrin eine regulierende Funktion auf die Mikrozirkulation der Magenschleimhaut ausüben.

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Fig. 4. Ratio (gastric mucosal blood flow [ml/min]/secretion rate [ml/min]) after treatment with 4 mg/kg burimamide (△) and 2.9 mg/kg metiamide (□). Difference between the last value before and those after metiamide is marked by x when significant at the 5% level.