

Effects of caseinomacropptide (CMP) on digestion regulation

M Yvon ¹, S Beucher ¹, P Guilloteau ²,
I Le Huerou-Luron ², T Corring ³

¹ INRA, Laboratoire de Recherches Laitières, Domaine de Vilvert, 78352 Jouy-en-Josas Cedex;

² INRA, Laboratoire du Jeune Ruminant, 35042 Rennes Cedex;

³ INRA Laboratoire d'Écologie et Physiologie du Système Digestif,
78352 Jouy-en-Josas Cedex, France

Summary — Caseinomacropptide (CMP) is a 64-amino-acid-residue peptide which is released from κ -casein by gastric proteinases. This review sums up the knowledge concerning its effects on the digestive function. Part 1 recalls the origin and heterogeneity of CMP. Here we underline that there are various forms of CMP which differ by their glycosylation level and genetic mutation. Consequently the forms used for studying biological activities need to be defined accurately. Part 2 summarizes the effects of CMP on digestive secretions. The major effect is an inhibitory effect on acid gastric secretions. Simultaneously, the blood concentration of regulatory digestive peptides is modified. In part 3 we try to clarify the mechanisms of action of CMP. A slightly glycosylated form of CMP, the A variant, appears to be responsible for the biological activity. Evidence suggests that CMP triggers stimuli from intestinal receptors without being absorbed. The signal would be then transmitted to organs through regulatory digestive peptides.

glycomacropptide / casein / digestive secretion / regulation / regulatory endogenous peptide

Résumé — **Effet du caséinomacropéptide (CMP) sur la régulation de la digestion.** *Le caséinomacropéptide (CMP) est un peptide de 64 résidus d'acides aminés libéré de la caséine κ par les protéases gastriques. Cette revue fait le point des connaissances sur ses activités de régulation de la fonction digestive. Dans une première partie nous rappelons l'origine et l'hétérogénéité du CMP, en soulignant qu'il existe plusieurs formes de CMP, qui se distinguent par leur niveau de glycosylation et par des mutations génétiques. Il est donc nécessaire de préciser les formes utilisées dans les études d'activités biologiques. La deuxième partie est une synthèse des activités du CMP sur les sécrétions digestives. Le principal effet est un effet inhibiteur sur les sécrétions acides gastriques. Parallèlement les taux sanguins des peptides régulateurs digestifs sont modifiés. Dans la troisième partie nous tentons d'élucider les mécanismes d'action du CMP. Une forme faiblement glycosylée du CMP variant A serait responsable de l'activité biologique. Ce CMP déclencherait des stimuli à partir de récepteurs intestinaux, sans être absorbé. Le signal serait ensuite transmis aux organes par l'intermédiaire de peptides régulateurs digestifs.*

glycomacropéptide / caséine / sécrétions acides gastriques / régulation / peptides régulateurs digestifs

INTRODUCTION

Digestive functions are regulated by a number of nervous and hormonal mechanisms triggered by the sight, smell and intake of a meal. The different constituents of the diet and their degradation products also have various effects on the digestive tract, which are related to these nervous and hormonal mechanisms. Thus, dietary proteins and their degradation products are involved in the physiological regulation of digestion. Furthermore, other more specific regulatory mechanisms associated with particular peptides can be involved. Thus, milk proteins contain several peptide segments, which can be released during digestion and may have a particular biological activity (Maubois and Léonil, 1989). These peptides may act either directly as neurotransmitters or indirectly by stimulating secretions of regulatory endogenous peptides from intestinal receptors. Caseinomacropptide (CMP), which is rapidly released during the gastric digestion of milk, might be one of these bioregulators. Several studies have shown its effects on digestive secretions and have tried to clarify its mechanism of action.

ORIGIN, PHYSICOCHEMICAL CHARACTERIZATION AND PROCEDURES TO ISOLATE CMP

Origin and heterogeneity of CMP

Cows' milk contains 2 groups of proteins, caseins, which are insoluble phosphoproteins at pH 4.6, and whey proteins. The casein fraction represents 80% of the total nitrogen and is made up of 4 major proteins α S1, α S2, β and κ caseins, the proportions of which are 38, 11, 38 and 13% respectively.

CMP is the first hydrolysis product resulting from the action of gastric proteinases (chymosin and/or pepsin) on κ -casein. The Phe₁₀₅-Met₁₀₆ bond of κ -casein is the only one to be hydrolyzed during the first stage of milk clotting. CMP is the 106-169 fragment of κ -casein, its isoelectric pH ranges between 4 and 5 and it does not contain any aromatic amino acid. Moreover, its amino-acid composition and its sugar content make it very polar, and thus highly soluble in an aqueous medium contrary to the residual fragment 1-105 of κ -casein, which is named κ -paracasein.

CMP contains all the post-translational modifications of κ -casein (phosphorylation and glycosylation) and the mutations of the genetic variants. Thereby, like κ -casein, CMP is a very heterogeneous fraction. Seven forms of κ -casein can be distinguished by electrophoresis and 9 forms by ion-exchange chromatography. These forms correspond to different sugar and phosphorus contents. Five potential sites of glycosylation have been identified on bovine CMP (Zevaco and Ribadeau Dumas, 1984) (fig 1) and 5 different carbohydrate chains have been evidenced (Saito and Itoh, 1992) (fig 2). Tri- and tetrasaccharides containing at least 1 molecule of sialic acid represent around 93% of the carbohydrate chains bound to CMP. However κ -casein glycosylation seems to occur at random and, consequently, different combinations are possible. On average, 40% of κ -casein is not at all glycosylated, 30% contains 1 or 2 sialic acids per mole, 18% contains 3 or 4, and 5% contains more than 5.

There are 2 major genetic variants of κ -casein which differ in 2 amino acids (Mercier *et al*, 1973). The Thr₁₃₆ and Asp₁₄₅ residues of the A variant are replaced by Ile and Ala respectively in the B variant. These mutations make the B variant more hydrophobic than the A variant. Moreover, the variants do not have the same level of glycosylation since, on the one hand, the

Thr₁₃₆ residue is a potential site of glycosylation and, on the other hand, the carbohydrate chains of the BB genotype contain more sialic acid than the other genotypes (Robitaille *et al*, 1991).

The CMP primary structure is relatively well preserved in the different species: sheeps, goats and buffalos share 71 – 84% of homology with bovine CMP; in humans and pigs, the percentage of homology

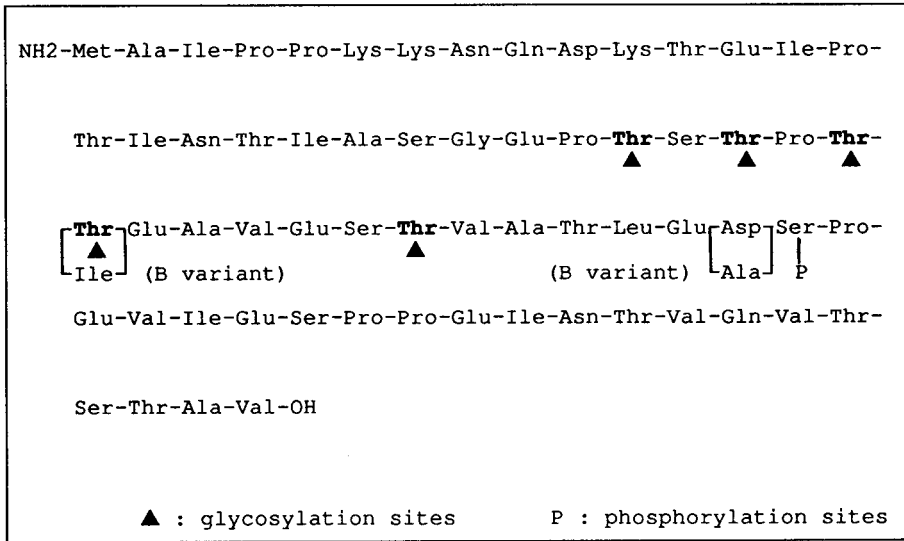


Fig 1. Primary structure of the A and B genetic variants of bovine caseinomacropptide.

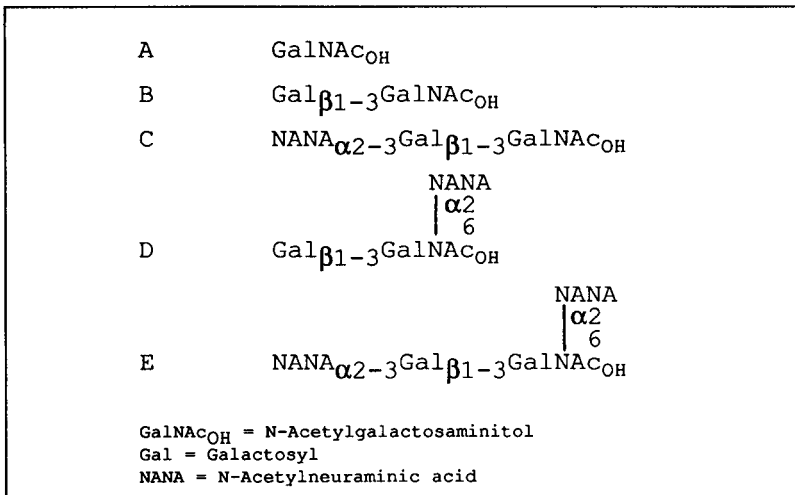


Fig 2. The complete chemical structure of the 5 carbohydrate units isolated from bovine normal κ-casein taken 3 months after parturition (Saito and Itoh, 1992).

reaches 55% (Mercier and Chobert, 1976). It should be noted that the 5 Thr residues that are binding sites for carbohydrate chains are well preserved and in particular the Thr residues located at positions 26 and 31 in bovine CMP, which are to be found in the 5 species mentioned above.

Methods of preparation of CMP for studying biological activity

CMP is generally prepared in the laboratory by controlled hydrolysis of free κ -casein by chymosin or pepsin. Residual protein and κ -paracasein are then eliminated by precipitation with trichloroacetic acid (TCA). Nevertheless, the heterogeneity of CMP causes differences in the solubility of its fractions in the presence of TCA. The glycosylated fractions remain soluble up to 12% TCA final concentration, whereas the non-glycosylated fraction precipitates from a concentration level of 4 or 5% and remains almost insoluble at 12% (Vreeman *et al*, 1986). As a result the 12% TCA soluble component is generally called glycomacropeptide (GMP). After elimination of TCA, this fraction (preparation 1) was used for several studies on biological activities in dogs and rats (Shlygin *et al*, 1971; Chernikov *et al*, 1974; Stan *et al*, 1974; Vasilevskaya *et al*, 1977; Chernikov *et al*, 1979). For some studies, a further fractionation was made on G-75 Sephadex (Stan *et al*, 1983) or G50 Sephadex (Aleinik *et al*, 1986). However, the fractions obtained and tested have never been characterized with accuracy as regards their glycosylation and phosphorylation levels or their genetic variants.

An industrial preparation (preparation 2) was used to study gastric secretions in the calf (Legeas, 1983; Guilloteau *et al*, 1986, 1994). The HPLC analysis of this product revealed that it contained the total CMP, *ie* the non-glycosylated and the glycosylated fractions of the 2 main genetic variants of

κ -casein (the A and B variants). Moreover, this product was slightly contaminated by the 1-23 fragment of α S1-casein.

Recently, in order to study pancreatic secretions in the pig, Beucher (1993) and Beucher *et al* (1994) have used the method developed by Savalle *et al* (1989), to prepare *in vitro* a hydrolysate similar to the digesta emptied from the calf abomasum during the 10 min following whole casein ingestion. The peptide fraction of the hydrolysate was separated from caseins by isoelectric precipitation (pH 4.6) of caseins, and then desalted by ultrafiltration. The total CMP represented about 70% of this peptide fraction, glycosylated CMP accounting for about half the total CMP. The A and B variants were found in the proportion 2:1. The contaminants consisted of a fragment of α S1-casein (1-23) and of β -lactoglobulin representing 20 and 7% respectively. This non-purified fraction (preparation 3) was used to measure pancreatic secretion in the pig. Moreover, these authors have further fractionated this preparation 3 by reverse-phase HPLC in order to study the release of cholecystokinin (CCK) in an isolated rat duodenojejunum. The non-glycosylated CMP of both A and B variants (CMP_A and CMP_B), the slightly glycosylated fractions of the same variants (GMP_{2A} and GMP_{2B}), and a mixture of highly glycosylated fractions of both variants, called GMP₂, were therefore isolated.

EFFECTS OF CMP ON THE DIGESTIVE FUNCTION

The role played by CMP on the digestive function has been studied by several teams since 1970. The first hypotheses were put forward by scientists from the Nutrition Institute of the Moscow Academy of Medicine, who emphasized the role of this peptide on gastric secretions in the newborn mammal after intestinal absorption under its quasi-

intact form. Since then, other teams have worked on this subject using different approaches.

In the following review, we have chosen to exclude observations made using whole casein or whole casein hydrolysates; the effects observed after intravenous injection of these products, especially vomiting and the inhibitory effects of the digestive myoelectrical activity (Vasilevskaya and Klimashima, 1979; Stan *et al*, 1983) seem to result from other peptides with an opiate activity (Stan *et al*, 1983, 1986; Stan and Ekimovsky, 1987).

Studies on the intact animal

Intravenous or parenteral infusions of CMP preparations

The intravenous or parenteral infusion of total GMP (preparation 1) inhibits the gastric acid secretion induced by different stimu-

lants, such as the gastrin C-terminal tetrapeptide, pentagastrin, histamine, and the administration of meat or bread, in dogs fitted with a Pavlov or Heidenein pouch (Shlygin *et al*, 1971; Chernikov *et al*, 1974; Vasilevskaya *et al*, 1977). On the contrary, it stimulates the secretion of gastric proteinases in dogs with a Heidenein pouch (Vasilevskaya *et al*, 1977). In these experiments, GMP were briefly infused and the quantities used varied considerably from one study to another (from 0.1 to 3.3 mg/kg LW). The response time was relatively long (1–2 h following infusion) (fig 3) and the effects lasted from 3–5 h. The inhibitory effect on gastric acid secretion was reproduced in rats using an isolated fraction of GMP (Stan *et al*, 1983). This effect could be in good agreement with the decrease in gastrin levels in the blood and in the antral tissue observed by Aleinik *et al* (1986). In this case, however, the quantities used (33–55 mg/kg LW) were higher than in dogs (particularly as it was a purified fraction) and the response time was only 30 min. Other

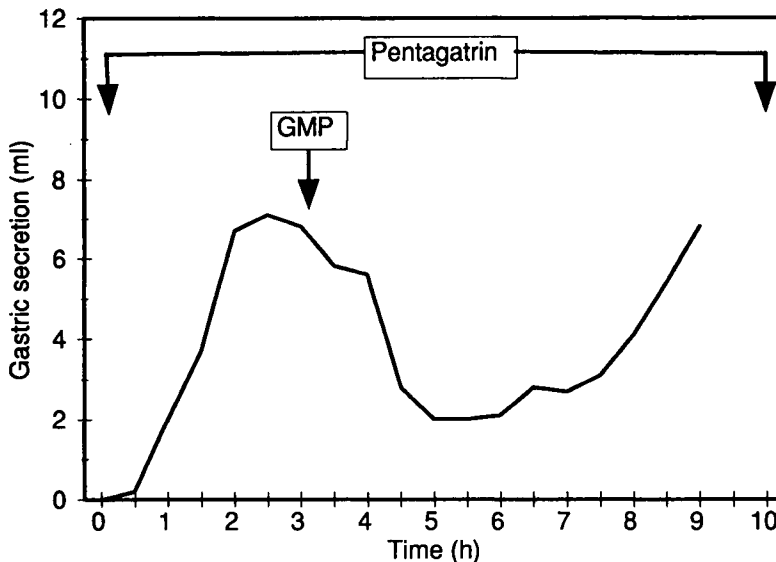


Fig 3. Effects of intravenous glycomacropeptide (GMP) infusion on gastric secretion stimulated by repeated infusion of pentagastrin (every 20 min) in dog (data from Vasilevskaya *et al*, 1977).

studies were made in preruminant calves fitted with a gastric pouch (developed by Guilloteau and Lecalve, 1977) and fed with a milk replacer based on CMP-free whey proteins. The intravenous infusion of CMP during the meal (preparation 2, at doses equal to 2 mg/kg LW) induced a slight decrease in the concentration of H⁺ ions in the abomasal secretion, but it did not lead to significant variations in the quantities of gastric secretions produced (juice, acids and enzymes) compared to control animals receiving no infusion or an infusion of physiological salt solution (Legeas, 1983; Guilloteau *et al*, 1986, and unpublished results).

Oral or enteral administration of CMP preparations

Acute experiments conducted on humans have shown that oral administration of 4 g of CMP (preparation 2) decreased by 15% the cumulated acid secretion after 30 min. This decrease was not due to the buffer effect of CMP, and such an effect was not observed at the level of 1 g (Bonfils and Roger, personal communication). When incorporated into calf food at the same level as in cows' milk (210 mg/kg LW), CMP (preparation 2) had an inhibitory effect on both gastric secretion (juice, acids and enzymes) and plasma concentrations of gastrin and especially CCK. These effects were observed during the first 2 h post prandial. By contrast somatostatin concentrations increased during the same period. Ingestion of CMP at a 5-fold higher level reduced or cancelled these effects (Legeas, 1983; Guilloteau *et al*, 1994, and unpublished results). In rats, jejunal perfusion of a fraction of CMP (at the level of 150 mg/kg LW) induced a decrease (by 38%) in gastric secretions (juice and acid) stimulated by pentagastrin, 25 min after the beginning of the perfusion (Aleinik *et al*, 1986). Lastly, the duodenal perfusion of preparation 3 of CMP in the pig for 30 min, at a level equal to

that emptied from the stomach during the first 10 min following a meal containing 16% casein (around 10 mg/kg LW), increased the flow of pancreatic juice and proteins 45–60 min after the beginning of the perfusion (fig 4) (Beucher, 1993).

Studies on isolated organs

Aleinik *et al* (1986) used the isolated and nerveless stomach of a previously anaesthetized young rat. The organ was immersed in a Krebs solution, the serous membrane was thus irrigated. Pentagastrin was added to stimulate acid secretion. Addition of a fraction of GMP at a level of 1 mg/ml in the immersion solution induced a 51% decrease in the stimulated acid secretion after 30 min.

The effects of CMP on CCK release have been studied using a model of isolated and vascularized rat duodenojejunum developed by Cuber *et al* (1989). This model was used for eliminating the other stimuli liable to be involved in the *in vivo* secretion. The intraluminal infusion of preparation 3 for 30 min, at a dose equal to that following a meal, immediately induced an increase in the CCK level in the blood, which reached a maximal value during the first 10 min; this level persisted throughout the infusion (Beucher *et al*, 1994). The response to the different isolated fractions of this preparation showed that this effect was mainly due to the poorly glycosylated fraction of the A variant.

STUDY OF THE MECHANISM OF ACTION OF CMP

It is difficult to review the results obtained by the different teams who have worked on 4 mammal species (rats, dogs, pigs and calves) using different approaches. The nature and doses of the products used vary considerably between the studies, and the

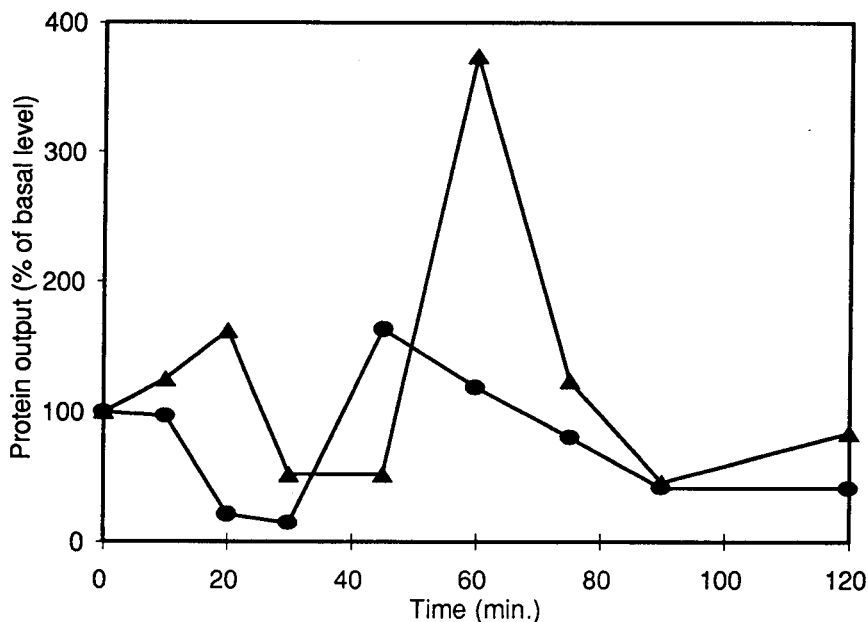


Fig 4. Effects of duodenal infusion of CMP preparation 3 (▲) and CMP-free casein (●) on the pancreatic protein output in pig expressed as percentage increase above the basal level (data from Beucher, 1993).

experimental protocols of the Russian research team often do not refer to any control treatment (infusion of physiological salt solution, *etc*). It is even more difficult to interpret and put forward hypotheses on the mechanisms involved since the measurements of the various digestive parameters and regulation factors have been performed in different species and using different protocols. However, from the results of these studies, it is possible to define the fractions of CMP responsible for the observed effects and to make assumptions concerning the mechanisms of regulation involved.

Identification of the active forms of CMP

The increase in pancreatic juice and proteins in the pig is not related to the protein mass of the fraction perfused into the intes-

nal lumen since administration of a 20-fold larger amount of CMP-free casein had no effect (Beucher, 1993). Moreover, the pancreatic secretion responses observed after duodenal infusion of different digesta are correlated to their CMP content (Beucher, 1993). In the calf the gastric secretion responses depend on the dietary proportion of CMP (Guilloteau *et al*, 1994) and the same applied to the man. CMP therefore appears to be responsible for the observed effects.

The nature of the CMP fraction seems to play a determining role. It can affect the response time. In the dog, for example, one fraction inhibits the acid secretion immediately after the intravenous infusion, whereas another fraction will have a response time ranging between 1.5 and 2 h (Stan *et al*, 1986). Two different fractions can have opposite effects on the acid secretion stim-

ulated by pentagastrin (Stan *et al*, 1983). However, the content of these fractions has neither been identified nor precisely characterized. By applying different hydrolysis treatments to GMP before intravenous injection (fig 5), Chernikov *et al* (1979) demonstrated that the whole CMP molecule is not necessary for peptide activity but that carbohydrate chains are essential. This was confirmed by Beucher *et al* (1994) who demonstrated that luminal infusion of the non-glycosylated fraction of the peptide into an isolated rat duodenojejunum had no effect on the release of CCK, unlike certain glycosylated forms.

The number of bound carbohydrate chains, their nature and binding site seem to be involved in the biological activity of the molecule (Beucher *et al*, 1994). The fraction containing the slightly glycosylated forms of the A variant of CMP, when perfused alone in the rat duodenojejunum,

highly stimulated the release of CCK. Most glycosylated forms were inactive. The B variant of CMP (which differs from the A variant only in 2 amino-acid residues) with a glycosylation level equivalent to the active fraction had no effect. Finally the presence of sialic acid at the extremity of the carbohydrate chains seems to be essential to CMP activity, since the removal of this residue eliminated the activity. However, the results obtained by Chernikov *et al* (1979) suggest that GMP desialylation does not modify its inhibitory effect on gastric secretions in the dog, but elimination of sialic acid residues (by controlled heat treatment) was not verified in this study. Thus, we can conclude that a minor form (< 20%) of CMP, processing on the Thr 21 carbohydrate chain that ends with a sialic acid, is responsible for the observed biological activities. It should be noticed that this Thr residue, specific of the A variant, is particularly well preserved in milk CMP from various species.

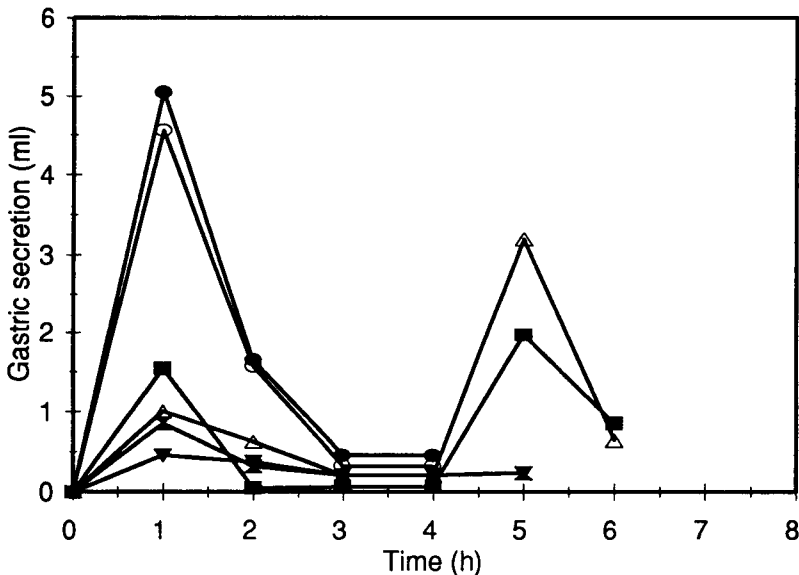


Fig 5. Effect of hydrolysis treatments of GMP on its ability to inhibit post-feeding gastric secretion in dog. CMP infusion made 1 h before the 100 g meat meal. Control (●): without GMP infusion; 1 (O): GMP after carbohydrates hydrolysis (2 N HCl, 110°C, 4 h); 2 (■): GMP without treatment; 3, 4 (X, Δ): GMP hydrolysed by trypsin and pepsin, respectively; 5 (▼): desialylated GMP (0.1 N HCl, 80°C, 90 min) (data From Chernikov *et al*, 1979).

Mechanisms of action of GMP

GMP thus seems to be responsible for the inhibitory effects of the stimulated acid secretions and for the increase in pancreatic secretions *in vivo*. Suppression of the vagal innervation or anaesthesia of the rat do not modify its inhibitory effect on gastric secretions in the rat. Aleinik *et al* (1986) have thus assumed that local cellular mechanisms might be involved. This hypothesis has been confirmed by showing that GMP can inhibit or stimulate secretions from isolated organs from rat (stomach and duodenojejunal loop) that are not, therefore, subjected to the influences of the central nervous system, or to the humoral system of the organism (Aleinik *et al*, 1986; Beucher *et al*, 1994).

Contrary to the hypotheses made by Chernikov *et al* (1979) and Aleinik *et al* (1986), it may not be necessary for the peptide or some active fragments to enter the blood to inhibit gastric secretion (Beucher *et al*, 1994). The rapidity of the response at the very beginning of the CMP infusion in the lumen of the rat intestinal loop suggests that the peptide absorption is probably unnecessary and that the stimulus is triggered on the mucous side of the intestinal cell. These hypotheses are supported by a much longer response time (30 min) when the peptide is in contact with the serous membrane of an isolated stomach (Aleinik *et al*, 1986). Moreover, the doses responsible for the effect in the intestinal loop (50 µg/ml, mucous side) are about 10 times lower than used in the stomach (400 µg/ml, serous side). Finally, considering experiments with intravenous infusion of CMP, it is difficult to believe that the latter might act as plasma ant gastrin under physiological conditions; the doses infused corresponded to plasma concentrations varying from 0.1 to 5 pmol/ml (and sometimes 65 pmol/ml) whereas the gastrin concentrations usually range between 0.015 and 0.1 pmol/ml. To confirm these results, it would be necessary to

define a GMP assay in the blood plasma and to measure its content after milk ingestion by a young mammal.

Therefore, GMP probably acts by triggering stimuli from intestinal receptors. The release of CCK produced by the I cells may be induced by a cholinergic mechanism, but according to Cuber *et al* (1990), the luminal nutrients act directly on I cells. By fixing directly on the luminal receptors, the GMP could favour the release of CCK. In the same way, it could have a direct influence on other endocrine cells of the digestive tract like D cells and G cells, producing somatostatin and gastrin, respectively. Its inhibitory effect on acid secretion and the level of gastrin could be related to a high somatostatin production (Guilloteau *et al*, 1994).

Considering the diversity of both the models used and the experimental protocols (method, digestive tract level, doses, *etc*), it is very difficult to link all the phenomena observed during the different studies. However, the results indicate that this peptide, resulting from the food protein digestion, probably plays a part in regulating digestion under physiological conditions.

CONCLUSION

GMP, which was identified in the gastric effluents of calves and newborn lambs immediately after milk or colostrum ingestion (Yvon and Pelissier, 1987; Yvon and Pelissier, 1993) thus appears to be a biologically active molecule. This raises the question of the biological significance of this peptide in a diet intended for young mammals, particularly as the primary structure of this peptide is relatively well preserved in the species. Given the importance of its inhibitory effects over the digestive function during the first hour following administration, its early release after meal ingestion in the gastrointestinal tract could attenuate the postfeeding stimulation of digestive

secretions and, consequently, enable the colostrum proteins such as lactoferrin and immunoglobulins to escape hydrolysis and play a role in the development of the intestinal flora and in the immunity of the young (Reiter, 1978).

GMP (in the intact or fragment form) could trigger stimuli from intestinal receptors without being absorbed. This would require the presence of carbohydrate chains containing sialic acid. The signal induced may be transmitted to organs *via* the stimulation or inhibition of the production of regulatory digestive peptides. Further studies will be necessary to validate these hypotheses. They should, in particular, define the structural characteristics affecting the peptide activity and demonstrate the presence of receptors in the intestinal mucous membrane. They should also demonstrate that the peptide is not absorbed and confirm its effect on the production of different regulatory digestive peptides (somatostatin, gastrin, secretin) by gastrointestinal cells using isolated organs or culture cells.

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