RAPID COMMUNICATION

Ghrelin and motilin: two sides of one coin?

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We would like to emphasize structural and effect-related similarities between the gastrointestinal hormone motilin, the recently discovered agent motilin-related peptide and a novel endogenous ligand of the growth hormone secretagogue receptor (GHS-R), ghrelin. In our opinion, the information summarized below indicates the existence of a family of gastrointestinal hormones linking endocrine control of energy balance and growth with the regulation of gastrointestinal motility.

A neuroendocrine system controls gastrointestinal motility at three different levels: the gut itself (enteric nervous system), the autonomic system and higher centers of the central nervous system (1). One way to quantify gastrointestinal motility is to measure the rate of gastric emptying. Gastric emptying depends on several factors: for example in hypoglycemia, rapid gastric emptying is observed (2, 3), whereas physiologic gastroparesis, resulting in impaired absorption of nutrients in the small bowel, has been described in hyperglycemia (4). It is not clear whether the effects of hyperglycemia on gastric motility are the aftermath of direct effects on the smooth muscle since smooth muscle contraction and relaxation are not affected by hyperglycemia *in vitro* (5). Moreover, foods with a high caloric content are emptied slowly from the stomach as compared with low caloric meals (5). The composition of a meal, (e.g. the proportion of fat, proteins and carbohydrates) is also believed to influence gastric emptying (5). Obviously, a close feed-back control regulation between the above mentioned parameters and the central nervous system exists in healthy individuals and could be disturbed in patients with a neuropathy of the enteric nerve system, (e.g. in patients with long-standing diabetes mellitus (4)). It is still unknown how information about composition and caloric content of a meal is signalled from the stomach to the central nervous system and *vice versa*. The new hormone ghrelin (6, 7) may participate in this putative regulatory feedback loop between the gastrointestinal tract and the central structures controlling food intake.

Recently Kojima and coworkers identified ghrelin as a ligand of the growth hormone secretagogue receptor (GHS-R) (6), based on its ability to induce GH secretion from pituitary cells. The 28 amino acid peptide hormone is characterized by an octanoyl side chain at serine 3 and its primarily secreted from distinct

endocrine cells in the stomach (8). The unique octanoylation feature appears to be essential for the hormone's bioactivity (at least as far as the stimulation of growth hormone secretion is concerned (6)).

Prepro-motilin-related peptide (prepro-MTLRP) was first described by Tomasetto and coworkers as a novel hormone originating from enteroendocrine cells of the stomach (9) and shares sequence and structural features with motilin. Despite its motilin like appearance, the authors summarize their findings as follows: 'The physiologic contribution of MTLRP to the endocrine regulation of important aspects of GI function such as contraction and/or acid secretion remains to be tested' (9).

Although the physiologic roles of motilin, MTLRP and ghrelin are not fully understood, we would like to point out the following facts that may extend the proposed role of this peptide family.

Effects on food intake

We have recently described that ghrelin, in addition to its role in regulating GH-secretion, induces adiposity *via* a central mechanism of increasing food intake and decreasing fat utilization (10). Similar findings, showing acute ghrelin induced stimulation of food intake confirm a role for ghrelin in the regulation of energy balance (11, 12, 13).

For more than a decade motilin also has been shown to have orexigenic effects (14, 15, 16).

Effects on growth hormone secretion

Ghrelin, as the first known endogenous ligand of the GHS-R stimulates GH secretion from pituitary cells with a potency similar to growth hormone releasing hormone (GHRH). This has been shown in several studies *in vitro*, in rodent models (6, 17) and in clinical studies (18–20).

Motilin has also been shown to be a potent growth hormone secretagogue (20, 21).

Structural similarities

Both ghrelin and MTLRP are synthesized in the stomach (6, 8, 9) although motilin is mainly expressed

Human Prepro-Ghrelin	1	M P S P G T V C S L L L L G M L W L D L A M A	23	
Human MTLRP		M P S P G T V C S L L L L G M L W L D L A M A		
Human Prepro-Motilin		M V S R K A V A A L L V V H V A A M - L A S Q	22	
Human Prepro-Ghrelin		G S S F L S P E H Q R V Q Q R K E S K K P P A	46	Human Prepro-Ghrelin
Human MTLRP		G S S F L S P E H Q R V Q Q R K E S K K P P A		Human MTLRP
Human Prepro-Motilin		T E A F V - P I F T Y G E L Q R M Q E K E R N	44	Human Prepro-Motilin
Human Prepro-Ghrelin		K L Q P R A L A G W L R P E D G G Q A E G A E	69	
Human MTLRP		K L Q P R A L A G W L R P E D G G Q A E G A E		
Human Prepro-Motilin		K G Q K K S L S V W Q R S G E E G P V D P A E	67	
Human Prepro-Ghrelin		D E L E V R F N A P F D V G I K L S G V Q Y Q	92	
Human MTLRP		D E L E V R F N A P F D V G I K L S G V Q Y Q		
Human Prepro-Motilin		P I R E E E N E M I K L T A P L E I G M R M N	90	
Human Prepro-Ghrelin		Q H S Q A L G K F L Q D I L W E E A K E A P A	115	
Human MTLRP		Q H S Q A L G K F L Q D I L W E E A K E A P A		
Human Prepro-Motilin		S R Q L E K Y P A T L E G L L S E M L P Q H A	113	
Human Prepro-Ghrelin		D K	117	
Human MTLRP		D K		
Human Prepro-Motilin		A K	115	

Figure 1 Comparison of amino residue sequences of ghrelin, MTLRP and motilin and their precursor-molecules. See also references (6), (9) and (29). *, an n-Octanoyl modified serine.

in the small intestine (23). The amino acid sequence of human prepro-MTLRP is identical with human prepro-ghrelin, except Serine 26 is not octanoylated in prepro MTLRP (6, 9). In addition, the human motilin-related peptide fragment [24–41] is identical with human Des-octanoyl³-ghrelin [1–18]. These observations indicate close structural relationships between motilin, motilin-related peptide and ghrelin as well as their respective precursor peptides (Fig. 1)

The gastrointestinal motilin receptor (MTL-R1A) and the GHS-R are both G-protein coupled receptors and show a high degree of structural homology (24, 25).

Involvement in the regulation of gastrointestinal motor activity

Motilin stimulates gastrointestinal motor activity in the antrum and upper duodenum and plays a key role in the regulation of interdigestive motility (26). There is evidence for the presence of motilin in various regions of the central nervous system (26).

Ghrelin stimulates gastric acid secretion and motility in rats and circulating ghrelin levels are correlated with gastric emptying time in humans (27, 28).

Conclusions

In conclusion, the gastrointestinal hormones motilin, MTLRP and ghrelin share not only structural properties regarding both the ligands as well as their G-protein coupled receptors but also appear to have comparable central and peripheral effects. Further studies should

address the question whether these similarities are only coincidental or if two endocrine systems that have been considered independent from each other are just two sides of the same coin.

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