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 feedback 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 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 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...
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.

### Acknowledgements

We would like to thank Todd M Suter, Indianapolis, for reviewing and editing the manuscript.

### References


Received 22 January 2001
Accepted 25 January 2001

www.eje.org