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GENERAL INTRODUCTION TO THE NINTH OLD HERBORN UNIVERSITY SEMINAR: GASTRO-INTESTINAL MOTILITY

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SUMMARY

Gastro-intestinal (GI) motility represents a complex, multifactorial interplay between factors deriving from the host, the food and the microbial flora. The intention is to break down food products into absorbable compounds and to excrete nonabsorbable compounds, bacteria, cell debris, etc.

The motility pattern differs markedly between the fasting and the postprandial state and is also influenced by the microbial status in various GI compartments. Direction and rate of flow of luminal contents depend on the force and frequency of stationary and propagated contractions.

This symposium is focused on three topics: 1. The motility itself; 2. The interplay between motility and the microbial flora; and 3. The influence of some antimicrobial agents on motility.

GI motility can be measured by many different methods. Pro's and con's related to these methods will also be discussed.

INTRODUCTION

The scope of the 9. Old Herborn University Seminar is defined by three task keywords: i) Motility, ii) Microflora, and iii) Methods. Hopefully, these task keywords will be looked upon from another 3M-point of view, i.e. at a i) Macroscopic, ii) Microscopic, and iii) Molecular level.

MOTILITY

According to Dorlands Illustrated Medical Dictionary, the term motility is defined as "the ability to move spontaneously". Motility is a basic prerequisite for all macroorganisms with a gastrointestinal tract. However, in spite of the simple definition given above, a close to 100 years old statement still holds true:

"On no subject in physiology do we meet with so many discrepancies of facts and opinions as in that of the physiology of the gastro-intestinal movements" (*Bayliss* and *Starling*, 1899).

Obviously, the discrepancies are caused by the complexity of the simple problem; how to move substances from mouth to anus? Any oral intake of any substance triggers a complex interplay between motility, secretion and absorp-

tion along the entire gastro-intestinal (GI) tract. Under physiological conditions, these processes are regulated by intrinsic and extrinsic nerves, and by a long series of polypeptide hormones. Principally, the same mechanisms are responsible for the coordination of GI motor and transport events during fasting. In fact, the events during fasting are even more complicated than during digestion. Gastric and intestinal motor and secretory functions are cyclically activated by intrinsic biological rhythms of enteric origin operating like coupled oscillators (*Wingate*, 1983). Thus, during fasting as well as during digestion, the GI tract acts as a functional unit in which the subunits oesophagus, stomach, duodenum, jejunum, ileum and colon are coordinated by stimulatory and inhibitory nervous and humoral mechanisms (*Ruppin*, 1985).

In an attempt to simplify this complex interplay, I will first focus upon some basic physiological cornerstones. The motor functions of the GI tract include mixing of dietary compounds with all kinds of secretory products from the body itself, followed by a propulsion of the content aborally (caudally).

Some parts of the GI tract are divided from the rest of the tract by sphincter mechanisms, so is the stomach and the large intestine. Sphincter mechanisms may also regulate the in-flow of endogenous secretion, as Sphincter Oddi.

The speed by which the content is passing through the various compartments is varying considerably. To give some perspective: transit through oesophagus is measured in seconds, whereas transit through the stomach is measured in minutes, through the small intestine in hours and through the colon in days.

The amount of content which is processed through the GI "pipeline" is also varying considerably. To give another perspective: it might be more than 10 litres a day through the duodenum, 1-2 litres through the very distal part of ileum and less than 500 ml or grams, through the rectum

The motility differs considerably throughout the GI tract, and in brief, it is as follows:

The oesophagus

The body of the oesophagus is normally relaxed and contracts in response to swallowing (primary peristalsis) or distension (secondary peristalsis). At the distal end of the oesophagus there is a sphincter mechanism, separating the positive gastric pressure from the negative oesophageal pressure. After initiation of either a primary or a secondary peristaltic wave there is a fall in lower oesophageal sphincter pressure which precedes the arrival of the peristaltic wave. Agents as gastrin, acetylcholine serotonin, prostaglandin F2-alpha and alpha-adrenergic agents increase the lower oesophageal sphincter pressure whereas secretin, cholecystokinin, vasoactive intestinal peptide (VIP), prostaglandin E1 and E2 and beta-adrenergic agents reduce the pressure.

The stomach

The stomach is a very muscular organ in which the food undergoes mixing and initial digestion. Peristaltic contraction waves sweep from the cardia to the duodenum. The stomach pumps its contents into the duodenum, the pump mechanisms comprises the distal portion of the gastric antrum, the pylorus and possibly the duodenal bulb. The mechanisms behind gastric motility will be described in greater details by the next speaker.

The small intestine

Contractions in the small intestine serve at least three different purposes. First, dietary products are mixed with the secretions of stomach, pancreas, biliary tract and small intestine. Second, the digestive products are brought into

intimate contact with the absorptive surface of the small intestine. Last, but not least, propulsive movements eliminate all kinds of nonabsorbable products, cell detritus and bacteria. The mechanisms behind small intestinal motility will be highlighted by the second speaker to come.

The large intestine

The motor functions include mixing, storage and slow propulsion of colonic content caudally, and a rapid, strong propulsion of content during defecation. Under physiological conditions, it is of importance that the colon does not initiate too rapid a transit. Colonic mixing and transit are mediated by several different types of contractions, and they seem to be under three levels of neural control: enteric, autonomic and central. These topics will be highlighted by the third lecture to follow.

MICROBES

The mere fact that germfree (GF) animals live as long as their conventional (CONV) counterparts does not implicate that presence of a gastrointestinal microflora has little, if anything, to do with gastro-intestinal motility. For scientists working with GF rats and mice, it is an everyday experience that the germfree GI tract demonstrates less spontaneous muscular contractions than their conventional counterparts. The enlargement of caecum, found in most species of germfree animals, still remains the main riddle of GF life.

A slower intestinal transit time in GF animals compared to their conventional counterparts was reported by several investigators almost 30 years ago (*Abrams* and *Bishop*, 1967; *Gustafsson* and *Norman*, 1969; *Ducluzeau* et al., 1970). Using the marker polyethylene glycol, *Heneghan* and *Mittelbronn* (1981) showed a reduced transit time in GF rats and dogs. They stressed the fact that the enlarged caecum in GF animals may represent a highly variable trap for a test meal, sometimes trapping large quantities, and other times small amounts.

The observation that caecal contents of GF rats and mice may contain a musculo-active substance (MAS) was also made almost 30 years ago (*Gordon*, 1967), and *Bruckner* (1997) describes the end of that story in this volume.

Utilising modern technology, *Caenepeel* and co-workers (1986; 1989) found less frequent migrating motor complexes (MMCs) in the small intestine of GF Fisher rats, when compared with the CONV counterparts, Caenepeel's findings have been extended by *Husebey* and co-workers (1990; 1992; 1994). These experiments show that the intestinal microflora represents a major stimulus for cyclic and aboral propagation of MMCs in the rat small intestine. Consequently, the resident microflora is a main factor in regulating fasting MMCs.

Rather few investigations are dealing with possible differences in colonic motor activities in GF and CONV animals. Several years ago, we investigated the caecum wall of GF and CONV rats with respect to the content of and sensitivity to some biologically active amines (*Strandberg* et al., 1966). The concentration of noradrenaline, l-adrenaline, dopamine, serotonin, acetylcholine and histamine was found to be of the same order of magnitude in both types of rats. Strips of the caecum wall from conventional rats exhibited regular spontaneous muscle contractions, whereas in germfree rats, such an activ-

Table 1: Total volume of endocrine immunoreactive cells in the gastro-intestinal tract of germfree rats

Immunoreactive cells	Fundus	Antrum	Jejunum	Ileum	Colon
Serotonin	↑	→	→	↑	↑
Motilin	∅	∅	→	↑	∅
Somatostatin	→	→	→	→	→
Neurotiensin	∅	∅	→	→	∅
Glucagon/glicentin	n.d.	n.d.	→	→	→
Gastrin	n.d.	↑	∅	∅	∅
Chromogranin A	→	n.d.	n.d.	n.d.	n.d.

↑ : increased
→ : no change
∅ : not supposed to be present
n.d. : not done

ity was never seen. In both GF and CONV rats, their type of a single contraction of the caecum strip as a response to the administered amines was similar except for serotonin. However, the threshold dose was generally higher in the GF rats than in the CONV rats, and the difference was most pronounced for acetylcholine. The caecum strip of a GF rat reacted to serotonin by contraction, initially rapid, then slowly proceeding to a maximum at about 2 minutes. The strips from the CONV rats reacted by rapid contractions.

The effects of age and microbial status upon muscular activity in caecum strips have also been evaluated (*Gustafsson* et al., 1970). Strips from 3-week-old GF and CONV rats showed the same - and low - muscular sensitivity to biogenic amines and had an absence of spontaneous activity. However, 8 weeks later, i.e. at 11 weeks of age, strips from CONV rats had the same high sensitivity and spontaneous muscular activity as in older CONV rats, whereas the strips from the GF rats reacted as those at 3 weeks of age. When young GF animals were conventionalized, i.e. were given aliquots of faecal suspension from CONV rats both by oral and rectal administration, their strips were after 8 weeks as sensitive to amines and reacted with the same spontaneous muscular activity as CONV rats of the same age. However, if one-year-old GF rats were conventionalized, no alterations in sensitivity or spontaneous activity were found after 8 weeks. The mechanism(s) behind this microbial, age-dependent "priming" of caecum motility remain(s) unknown - and may deserve some comments. *In utero*, the intestinal movements of the foetus are thought to be low. The intestine is filled with meconium, to be excreted after birth. If an excretion of meconium is not established some few days after birth, a search for reasons for this delay has to be undertaken - and most often, it is found to be a mechanical one. The establishment of GI motility - as well as other intestinal functions - is initiated and regulated by several, intrinsic as well as extrinsic, factors. The most dominating extrinsic factors are obviously food and establishment of an intestinal flora. Human milk contains high concentrations of several neuropeptides which can be absorbed in an

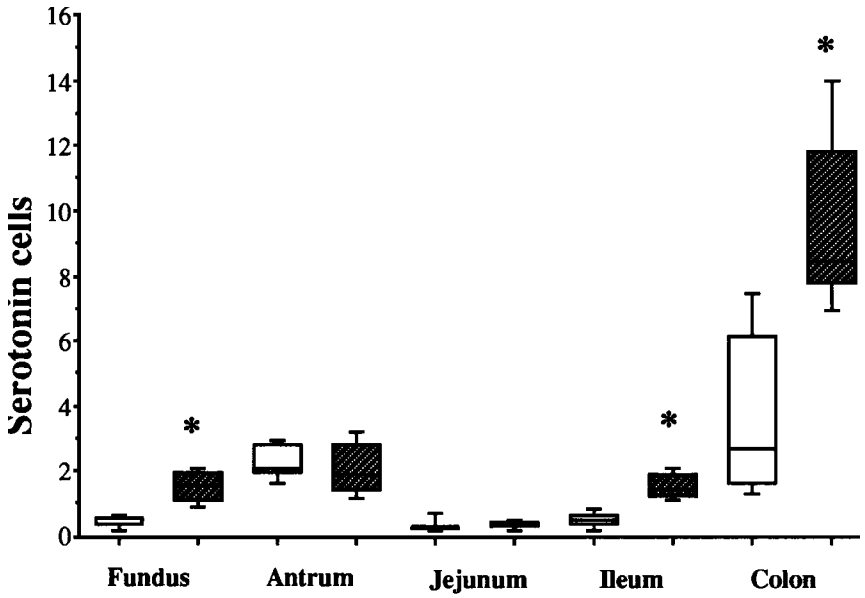

Figure 1: Total volume of serotonin immunoreactive cells in the gastro-intestinal mucosa of conventional (□) and germfree (▨) rats (*: $p<0.05$).

intact molecular form (*Werner* et al., 1985). It has also been found that formula-fed infants have higher basal levels of motilin than breast-fed infants (*Lucas* et al., 1980). It is well known that the intestinal flora in formula-fed infants differed markedly from the flora found in breast-fed infants. It is tempting to speculate that variations in diet may create variations in the microflora, thereby creating variations in the flora-associated influences upon GI peptides and motility.

We have recently investigated the volumes of endocrine cells in the GI tract of GF and CONV animals (*Alam*, 1995; *Uribe* et al., 1994), and some of our data is given in Table 1 and Figure 1. Previously it was known that considerable amounts of serotonin are present in the gut lumen (*Ahlman* et al., 1981) and that several microbial species can produce serotonin *in vitro* (*Karlsson* et al., 1988). If this occurs also *in vivo*, it will contribute to the luminal concentration of serotonin. It might then be reasonable to assume that a reduced availability of this amine, as in GF conditions, could trigger endogenous regulatory mechanisms to give rise to the hyperplasia or increased activity of serotonin-producing cells.

It is well known that endocrine cells producing serotonin may also produce motilin (*Polak* et al., 1975). Therefore the increase in motilin in GF rats might be secondary to the increase in serotonin. Another explanation might be that the increase in motilin represents a physiological up-regulation of intestinal motility in GF rats. However, as underlined before, the molecular mechanisms being the reduced GI motility in GF rats compared to their CONV counterparts are unknown (*Midtvedt*, 1989).

The clinical observation that antibiotic therapy may cause marked alterations in GI motility (from vomiting to diarrhoea) is well known indeed. In part, these alterations are due to alterations in the resident microbial flora.

However, it is also well established that several types of antibiotics have an inhibitory effect on smooth muscle contractility *in vitro*. (*Popovici* et al., 1965; *Paradelis*, 1981; *Koeda* et al., 1982). In the last decade, most attention has been paid to the macrolide group of antibiotics and effects upon GI motility. The findings by *Klika* and *Goodman* (1982) that erythromycin acted directly, i.e. not via the microbial flora, upon the motility, prompted a long series of investigations concerning the influence of antibiotics upon intestinal motility. (For reviews see: *Midtvedt* 1989; *Midtvedt* and *Greenwood* 1994; *Midtvedt* and *Greenwood*, 1995).

METHODS

The ways of observing GI motility includes a long series of different methods, from naked-eye inspection, transit time, x-ray examination, ultrasonic investigation, internal pressure curves, electromyography, etc. The following papers will discus the pro's and con's about some of the clinical and experimental methods currently in use.

LITERATURE

Ahlman, H., Bhargava, H.N., Dahlström, A., Larsson, I., Newson, B., and Pettersson, G.: On the presence of serotonin in the gut lumen and possible release mechanisms. Acta Physiol. Scand. 112, 263-269 (1981).

Alam, M.: Modulation of gastrointestinal cell kinetics and endocrine cell populations by the microflora and endogenous prostaglandins. An experimental study in germfree and conventional rats. Doctoral thesis, Reproprint AB, Stockholm, Sweden (1995).

Abrams, G.D. and Bishop, J.E.: Effect of the normal microbial flora on gastrointestinal motility. Proc. Soc. Exp. Biol. Med. 126, 301-304 (1967).

Bayliss, W.M. and Starling, E.H.: The movement and innervation of the small intestine. J. Physiol. (London), 24, 99-143 (1899).

Bruckner, G.: How it started - And what is MAS? In: Gastro-intestinal motility. Old Herborn University Seminar Monograph 9 (Eds.: Heidt, P.J., Rusch, V., and van der Waaij, D.). Herborn Litterae Verlag wissenschaftlicher Schriften und Bücher, Herborn, 25-35 (1997).

Caenepeel, P.H., Janssens, J., Vantrappen, G., Eyssen, H. and Coremans, G.: Interdigestive electrical activity and transit in germfree rats. Data presented at the Meeting on Frontiers in Microbiology, Leuven (1986).

Caenepeel, P.H., Janssens, J., Vantrappen, G., Eyssen, H., and Coremans, G.: Interdigestive myoelectric complex in germ-free rats. Dig. Dis. Sci. 34, 1180-1184 (1989).

Ducluzeau, R., Bellier, M., and Raibaud P.: Transit digestif de divers inoculums bactériens introduits "per os" chez des souris axeniques et "holoxeniques" (conventionelles): Effect antagoniste de la microflore du tractus gastro-intestinal. Zentralbl. Bakteriol. 213, 533-548 (1990).

Gordon, H. A.: A substance acting on smooth muscle in intestinal contents of germfree animals. Ann. N. Y. Acad. Sci. 147, 83-106 (1967).

Gustafsson, B.E. and Norman, A.: Influence of the diet on the turnover of bile acids in germ-free and conventional rats. Br. J. Nutr. 23, 429-442 (1969).

Gustafsson, B.E., Midtvedt, T., and Norman, A.: Effects of microbial contamination on the cecum enlargement of germfree rats. Scand. J. Gastroent. 5, 309-314 (1970).

Heneghan, J.B. and Mittelbronn, M.Y.: Vitamin B-12 absorption in cecectomized gnotobiotic rats. In: Proceedings of the 28th International Congress of Physiological Sciences, Budapest (Eds.: Gati, T., Szollar,

L.G., and Ungvary, Gy.). Advances in Physiological Sciences: Nutrition, Digestion, Metabolism 12, 453-457 (1981).

Husebye, E., Hellström, P.M., and Midtvedt, T.: The role of the normal microbial flora in the control of small intestine motility. Microecol. Ther. 20, 389-394 (1990).

Husebye, E., Hellström, P.M., and Midtvedt, T.: Introduction of conventional microbial flora to germfree rats increases the frequency of migrating myoelectric complexes. J. Gastrointest. Mot. 4, 39-45 (1992).

Husebye, E., Hellström, P.M., and Midtvedt, T.: Intestinal microflora stimulates myoelectric activity of rat small intestine by promoting cyclic initiation and aboral propagation of migrating myoelectric complex. Dig. Dis. Sci. 39, 946-956.

Karlsson, S., Banhidi, Z.G., and Albrektsson, A.-C.: Detection by high-performance liquid chromatography of polyamines formed by Clostridial putrefaction of caseins. J. Chromatogr. 442, 267-277 (1988).

Klika, L.J. and Goodman, J.M.: Gastrointestinal tract symptoms from intravenously administered erythromycin. J. Am. Med. Ass. 248, 1309 (Letter) (1982).

Koeda, T., Umemura, K., and Yokota, M.: Toxicology and pharmacology of aminoglycoside antibiotics. In: Aminoglycoside antibiotics (Eds.: Umezawa, H. and Hooper, I.R.). Springer-Verlag, Berlin (1982).

Lucas, A., Blackburn, A.M., Aynsley-Green, A., Sarson, D.L., Adrian, T.E., and Bloom, S.R.: Breast vs. bottle: Endocrine responses are different with formula feeding. Lancet I, 1267-1269 (1980).

Midtvedt, T.: The normal microflora, intestinal motility and influence of antibiotics. An overview. In: The regulatory and protective role of the normal microflora. Wenner-Gren International Symposium Series 26 (Eds.: Grubb, R., Midtvedt, T., and Norin, E.). MacMillan Press Ltd., Houndmills, Basingstoke, Hampshire, London, 147-167 (1989).

Midtvedt, T.: Miscellaneous antibiotics. In: Side Effects of Drugs Annual 13 (Eds.: Dukes, M.N.G. and Beeley, L.). Elsevier Science Publishers B.V. (Biomedical Division), Amsterdam, London, New York, Tokyo, 220-229 (1989).

Midtvedt, T. and Greenwood, D.: Miscellaneous antibacterial drugs. In: Side Effects of Drugs Annual 17 (Eds.: Aronson, J.K. and van Boxtel, C.J.). Elsevier Science Publishers B.V. (Biomedical Division), Amsterdam, London, New York, Tokyo, 303-318 (1994).

Midtvedt, T. and Greenwood, D.: Miscellaneous antibacterial drugs. In: Side Effects of Drugs Annual 18. (Eds.: Aronson, J.K. and van Boxtel, C.J.). Elsevier Science B.V. (Biomedicine), Amsterdam, London, New York, Tokyo, 306-315 (1995).

Paradelis, A.G.: Inhibition of the pendular movements of the intestine by aminoglycoside antibiotics. Methods and Findings in Exp. and Clin. Pharmacol. 3, 173-177 (1981).

Polak, J.M., Pearse, A.G.E., and Heath, C.M.: Complete identification of endocrine cells in the gastrointestinal tract using semi-thin sections to identify motilin cells in human and animal intestine. Gut 16, 225-229 (1975).

Popovici, G.G., Moisa, L., Negoita, M., Manoila, V., Botez, E., Hafner, R., and Gumeni, N.: The influence of certain antibiotics on intestinal motor activity. Arch. Int. Pharmacodyn. Ther. 154, 374-381 (1965).

Ruppin, H.: Current aspects of intestinal motility and transport. Klin. Wochenschrift 65, 679-688 (1985).

Strandberg, K., Sedvall, G., Midtvedt, T., and Gustafsson, B.E.: Effect of some biologically active amines on the cecum wall of germfree rats. Proc. Soc. Exp. Biol. & Med. 121, 699-702 (1966).

Uribe, A., Alam, M., Johansson, O., Midtvedt, T., and Theodorsson, E.: Microflora modulates endocrine cells in the gastrointestinal mucosa of the rat. Gastroenterology 107, 1259-1269 (1994).

Werner, H., Koch, Y., Fridkin, M., Fahrenkrug, J., and Gozes, I.: High levels of vasoactive intestinal peptide in human milk. Biochem. Biophys. Res. Comm. 133, 228-232 (1985).

Wingate, D.L.: Complex clocks. Dig. Dis. Sci. 28, 1133-1140 (1983).