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Review article

Forty years of achievement in French research on digestive physiology in the pig

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Abstract — The contribution of the research group set up by Rérat in the early 1960s in Jouy-en-Josas, and then expanded to Rennes, is summarised. As digestive processes are a major key to the nutritional status of monogastric animals, original methodologies based on advanced experimental surgery were developed in the pig to quantify the digestion and absorption yield, to know their factors of variation, and to understand their physiological and nutritional consequences. The group also extended its expertise to the control of food intake, the role of the nervous system and regulatory peptides, and several biomedical gut-related topics.

pig / digestion / absorption / neurohumoral regulation / adaptation

Résumé — Réalisations et succès de la recherche française : quarante ans de physiologie digestive chez le porc. Dès le début des années 60, un groupe de recherches a été constitué à l'initiative de A. Rérat à Jouy-en-Josas pour étudier divers aspects de la physiologie digestive chez le porc. Leur exploration a fourni des clés essentielles pour la maîtrise du statut nutritionnel chez cette espèce monogastrique, et un instrument d'amélioration de la production porcine. Ce groupe s'est élargi au fil des années et a même essaimé dans les années 80, notamment à Rennes. Il a apporté une contribution essentielle par le développement de méthodologies nouvelles généralement basées sur une chirurgie expérimentale très élaborée. Ces approches ont fourni de nombreux travaux originaux qui ont permis de décrire les processus de digestion (motricité, transit, sécrétions, hydrolyses enzymatiques et fermentations) et d'absorption, d'en quantifier le rendement, d'en étudier les possibilités d'adaptation, et d'en apprécier les conséquences nutritionnelles. Le groupe a étendu son expertise à la physiologie de l'ingestion, au rôle du système nerveux entérique et central et à celui des peptides régulateurs. Ses compétences ont également été mises à profit pour aborder diverses recherches biomédicales concernant le tube digestif.

porc / digestion / absorption / régulation neurohumorale / adaptation

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1. INTRODUCTION

In order to base the improvement of overall growth on a better knowledge of nutritional requirements in growing pigs, from the 1960s onwards Rérat headed the progressive enlargement of a specialised research team. As the efficiency of digestive processes is a major key to the nutritional status in monogastric animals, the group explored several physiological functions such as gastrointestinal motility and food passage, digestive enzyme secretions, luminal digestion and intestinal absorption, intestinal and hepatic handling of nutrients, neurohumoral control of food intake and digestive processes. Further developments also concerned human-oriented biomedical research.

At the beginning, exploratory studies were performed by Rérat to reevaluate the techniques formerly used in various animal species, such as the gut fistulation technique [4], or methods for the collection of pancreatic juice [179]. Thus he obtained a first description of food passage in the digestive tract [6, 146]. He also founded the basis for a direct quantitative measurement of nutrient absorption with the development of portal vein catheterisation [3] and portal blood flow measurement [140], and initiated the pancreatic duct fistulation technique [13, 139] which opened the way for the study of pancreatic secretion [32, 33]. These preliminary studies were then extended through the development of original techniques based on advanced experimental surgery allowing physiological studies in conscious animals. The major steps are reviewed thereafter.

2. UNDERSTANDING GASTROINTESTINAL MOTILITY IN THE PIG

Recently developed in sheep [171], electromyography applied to gastrointestinal smooth muscle was then used in conscious pigs [87]. Over the 1970–1985 period this technique allowed us to reexamine the respective properties of the gastrointestinal muscle layers of the stomach and small intestine, i.e. the cellular and tissue electrical characteristics [98, 108], and to describe the organisation of the electrical activities over time and over the whole organ [96, 103, 104]. We then tried to provide preliminary explanations for the general assumption that food passage results from gastrointestinal motility. The overall organisation of motility along the tract in relation with feeding [96] and the relationship with the flow of digesta in normal or pathological conditions were investigated [97, 98, 108].

2.1. Myogenic organisation of gastric and intestinal motility

As regards the stomach, a periodic oscillation (rapid depolarisation) of membrane potential (3.8 min^{-1}) occurs from pacemaker cells near the cardia and propagates at an increasing speed (0.5 to 2 $cm{\cdot}s^{-1}$) towards the pylorus. This is referred to as electrical control activity (ECA) and may be accompanied, in the case where a contraction occurs, by an electrical response activity (ERA) whose duration and amplitude correlate with the duration and amplitude of the contraction. It means that the maximum frequency of gastric contractions at any point of the gastric muscle is determined by the basic ECA mean rate (i.e. 3.8 min^{-1}). The ERA and associated contraction may be local or follow the aboral propagation of the ECA. Therefore contractions, when they occur, may be either local or propagated over a variable length of the gastric body and antrum at an increasing speed. These basic mechanisms might account for the regular mixing movements of gastric contents as well as for the deep waves propelling contents towards the distal antrum and ending with the sudden closure of the pylorus when reached by the contraction.

The small intestine muscle also exhibits an intrinsic permanent electrical rythm, without any mechanical significance. This periodic oscillation of the membrane potential of the smooth muscle is a slow potential variation known as slow wave and occurring as a pseudo-sinusoidal event. The slow waves originate from several pacemaker locations, the proximal location being dominant on the more distal sources. This results in a proximodistal decreasing gradient of slow wave rythm, from 17 to 18 min^{-1} on the proximal duodenum to 11 min^{-1} on the terminal ileum. In parallel, the slow waves propagate in the proximo-distal direction, with values ranging from about 80 to 20 $mm \cdot s^{-1}$, and may elicit the discharge of spikes. Thus when a contraction occurs, more or less dense groups of spike potentials are superimposed on the slow waves. There is a coordination between the longitudinal and circular layers, the latter producing the largest number of spikes when a contraction occurs. In all cases the spikes can occur only during a fixed part of the cycle of slow waves which act as a pacesetter for the spike bursts. It means that the maximum frequency of the small intestine contractions at a given point is fixed by the local rythm of the slow waves, and that their apparent propagation occurs at a velocity determined by the rate of slow wave propagation (i.e. a few $cm \cdot s^{-1}$).

2.2. Pattern of motility and digesta flow

These basic mechanisms can be organised in different ways to produce different intestinal myoelectric and motor patterns: isolated local contractions and contractions propagated over a variable distance (peristaltic waves) occurring within an irregular spiking activity (ISA), and multiple local rythmic contractions forming a regular spiking activity (RSA) over a whole segment of intestine at a given time (rythmic segmentation). These different forms of motility organisation occur within an overall pattern of sequences known as the myoelectric or motor migrating complex (MMC), regularly recurring from the proximal duodenum and slowly migrating distally along the small intestine (from 300 $mm \cdot min^{-1}$ in the proximal area to 50 $mm \cdot min^{-1}$ in the distal area). MMC includes a quiescent phase, an ISA phase, and a brief (3–4 min) RSA phase. The systematic study of these MMCs showed that 2 to 3 complexes are permanently present along the pig small bowel. The average number of MMCs per 24 h is around 20 on the duodenum, 16 in the jejunum and 11 in the ileum as 40% of them do not migrate along the whole intestine. The average recurrence interval ranges at around 70 min in the duodenum and 110–120 min in the ileum.

However these values vary according to different factors. The relative duration of quiescence increases at the expense of the ISA during the overnight fast; on the contrary, a continuous ISA phase occurs in the proximal intestine during 2–3 h after a large meal. Moreover, the MMC pattern may be modified depending on the diet (coarse vs. purified) suggesting a relationship between MMC pattern and food passage. We established that digesta flux occurred during the ISA phase while the subsequent RSA acts as a barrier avoiding backflow. A quiescent phase is then recorded on an emptied intestinal segment. Thus food passage occurs as batches of digesta propelled within the length of the segment concerned with an ISA phase. This therefore occurs at an average rate determined by the migration rate of MMC which acts as a cruise control system. The resulting duration of the proximo-distal passage of digesta into the small intestine is approximately 120 min. This relationship between digesta passage and the MMC pattern was further supported under different conditions, either dietary (lactose feeding) or experimental (overloading the digestive lumen with additional digesta or depleting it by external derivation).

Electromyography in conscious pigs thus allowed a better understanding of the myogenic organisation of gastrointestinal motility in pigs: contractility of the smooth muscle cells and origin of rythmicity and polarity, coordination within the muscle layers, overall pattern for each organ, and global knowledge of the relationship between motility and food passage. However, for several physical (mechanical) reasons, electromyography did not allow a detailed analysis of the relation between the movements of underlying contents and the actual strength of contractions. The time came for miniature strain gages and multilumen tubes. But in order to assess nutrition in pigs, we preferred direct quantitative and qualitative approaches to food passage and digestion, beginning with fistulation techniques, and ending with gamma scintigraphy [123].

3. MOTOR AND SECRETORY COORDINATION IN THE GASTRODUODENAL AREA

The physico-chemical conditions within the gut lumen result from the confluence and interaction of several sources. The gastric, pancreatic, biliary and intestinal secretions are of importance for the kinetics of digestion. Together with digesta, they might determine the pH of digestive contents which might in turn trigger various neurohumoral events able to modify or modulate both motility and secretions. Though the meal induces a typical change, in situ studies of intragastric pH showed indeed that the characteristics of the diet are of minor importance in comparison with those of gastric acid secretion [89, 106]. Within the duodenum, bile and pancreatic juice play only a minimal role in the neutralisation of the large quantities of digesta flowing from the stomach during the postprandial ISA phase in fed pigs. On the contrary, in fasted pigs, they highly contribute to the neutralisation of the gastric acid effluent and to maintaining the pH at values higher than 6 for more than 60% of the time [1].

This supported the hypothesis of a close coordination between duodenal motility and bile excretion, formerly proposed on the basis of simultaneous bile flow recording and bile duct (including Oddi) electromyography [93, 94]. Further experiments led us to conclude that a true biliary and pancreatic secretory component of MMC exists in the pig [2]. Bile secretion is always minimal during duodenal quiescence, and increases after the start of the ISA phase to reach a maximum at the beginning of the RSA phase, i.e. 2- to 3-fold higher than the basal flow during quiescence. Pancreatic secretion was also very low (about 3 drops·min^{-1}) during duodenal quiescence, markedly increased during the ISA phase, and reached a maximum (around 48 drops·min^{-1}) at the onset of the RSA phase. However, the major role of the gastric acid outflow to determine the cyclical variation of intraduodenal pH, and the role of bile and pancreatic secretions in the neutralisation of the duodenal chyme were simultaneously confirmed, as the cyclical variation of pH took place within a much more acid range during biliary and pancreatic diversion [2].

We speculated on whether fluctuations in secretion and pH were responsible for the MMC phases or whether it was the reverse, and on the possible mediation of some regulatory peptides. The acidification of the proximal duodenum was previously shown to induce the release of secretin and motilin in anaesthetised pigs [43]. A temporal relationship was evidenced in conscious fasting pigs between the successive phases of MMC and the cyclical variation of plasma motilin, pancreatic polypeptide, and gastrin, but not somatostatin [42, 44]. Nevertheless the variations of plasma motilin are only of sufficient magnitude to possibly result in significant effects on duodenal motility in the pig.

4. DIGESTIVE SECRETIONS AND ADAPTATIONS TO THE DIET

As they play a determining role in the enzymatic digestion of food, pancreatic and biliary secretions received sustained attention, both in terms of their fundamental physiology under well defined nutritional conditions (diet composition, meal frequency), and of their modifications due to various nutritional factors. These studies were mainly based on permanent fistulation techniques allowing continuous collection, sampling and restitution of the secretions [27]: permanent pancreatic duct fistulation [33] and bile duct fistulation [78]. The Pr. Desnuelle group in Marseille, using the lyophilised pancreatic juice we collected in Jouy-en-Josas, obtained for the first time in the pig some purified pancreatic enzymes (colipase, chymotrypsine) for biochemical studies [23, 125]. This was the onset of several developments. Salivary secretions will not be considered in this paper. As regards intestinal carbohydrases, let us just note that they are age- and diet-dependent: an increase in the activity of both sucrase and maltase has been described in the young pig [9], while endogeneous and exogeneous (microbial) lactase responded to an excess of lactose in the diet [17].

4.1. Pancreatic secretion

During neonatal life, the biosynthesis of pancreatic enzymes has been studied in the pig using different approaches carried out on tissue homogenates. The pancreatic secretion is rich in proteolytic, lipolytic and amylolytic enzymes. The age at which these enzymes are produced in sufficient amount is of importance e.g. amylase, to determine an optimal replacement of maternal milk by a starchy diet. Studies conducted in the piglet from birth to 8 weeks [34] described the progressive development of enzymatic equipment according to age, particularly showing the early appearance of chymotrypsin (one week) and lipase (two weeks), later followed by amylase (one month), which makes an early weaning with starchy feeds difficult. This increased secretion of various enzymes with age does not seem to depend on dietary changes due to weaning but to a variation in the neuroendocrinological balance.

In growing animals, the fistulation techniques allowed to describe the nycthemeral variations in pancreatic secretion and the strong stimulation (2.5 to 3 times) due to the meal intake [32, 33]. Moreover, the composition of the diet influences tissue levels and secretions of enzymes. Aumaitre and Rérat [11, 12] first observed that the quantitative production of amylase increased in the presence of increased starch intake, and that the in vitro lipase activity varied according to the nature of lipid substrates. This is also true for chymotrypsin whose production varies with the quality and level of protein in the diet [8, 10]. Indeed the proportions of the different groups of enzymes vary according to the proportion of the various dietary components, resulting in an adaptation of the enzyme to its substrate.

Data demonstrated that for a constant enzymatic output, the pancreas of the growing pig responded to an increase in the protein content of the diet by a significant rise in the activity of chymotrypsin [29]. A significant increase in the activity of proteases in the pancreatic juice has also been observed in the presence of high amounts of rapeseed meal in the diet [180]. Similarly, in the piglet, a marked increase in the activity of trypsin and chymotrypsin has been observed during suckling time [34], and in Elastase I at the expense of Elastase II [66]. Other data demonstrated a low activity of trypsin and chymotrysin in the pancreas of weaned piglets fed hydrolysed soluble fish protein concentrate [18, 130].

Adaptation also occurs for amylase and lipase-colipase when the diet is enriched by starch and lipids, respectively [25]. The activity of pancreatic lipase responded to an increase in the dietary fat level in the growing pig [129]. Such an increase has been observed at the expense of the activity of amylase when the level of dietary tallow was increased in the diet of the weaned piglet [138]. But conversely, no difference in lipase activity was observed according to the source of fat: tallow vs. olive oil, when fed to animals of different breeds [20].

Accordingly, the regulation of exocrine pancreatic secretion partly depends on nutritional conditions. It is a qualitative, long-term adaptation since the new enzyme pattern occurs within 2–3 days and stabilises within 5–7 days. The mechanisms of this regulation still remain controversial. However, enzyme adaptation seems to be partly related to changes in the amounts of hydrolysis products present in the small bowel due to variations in the dietary supply [173], via a substance produced by the duodenal mucosa [174]. It must be underlined that total dietary protein deprivation results in a reduction in the amount and chronology of enzyme production from the pancreas [37], particularly concerning chymotrypsin after one week, and later on and to a lower extent amylase and lipase. But the protein secretion was neither quantitatively nor chemically modified.

Exocrine pancreatic secretion is also subjected to another regulation, i.e. a quantitative and short-term regulation [24]. The exclusion of pancreatic enzymes from the intestinal lumen immediately causes a stimulation of total pancreatic secretion; their re-introduction results in the re-establishment of a normal secretion level. This regulation by negative feedback may explain the kinetics of pancreatic secretion during the digestion of a meal since, during the postprandial period, the enzymes become bound to the dietary substrates that they are hydrolysing, and hence cannot inhibit pancreatic secretion. It is only after hydrolysis that the liberated enzymes may ensure the regulation of secretion. This is also true after the intake of trypsin inhibitors, with pancreatic hypersecretion mainly affecting chymotrypsin and trypsin: Antinutritional factors in the diets of piglets increase the biosynthesis of chymotrypsin when antitryptic factors significantly decrease the activity of this enzyme [19, 121].

As a general conclusion, the age of the pig (namely the piglet) and the composition of the diet are responsible for a significant digestive adaptation by acting as ontogenic factors of the biosynthesis of pancreatic and intestinal enzymes [18, 26]. Pancreatic secretion plays an important role in digestion as a whole. After derivation of the pancreatic juice or after ligature of the pancreatic duct for a long time, protein digestibility is highly reduced (35%), more than energy digestibility [30, 31]. Carbohydrate and amino acid absorption are highly depressed, as shown by quantitative studies of absorption [151, 169]. However, on the long term, the level of deficiency tends to decrease, which may be due to a compensatory secretion of intestinal enzymes, or may be of bacterial origin [36].

4.2. Bile secretion

The kinetics of bile secretion was also studied in pigs with a permanent fistulation of the bile duct [78] for extracorporeal derivation of bile, thus allowing the measurement of volume and bile salts secreted. To preserve the normal enterohepatic cycle, bile was reinfused through a permanent fistulation of the duodenum. A specific apparatus was developed to make the duodenal restitution as identical as possible to the bile outflow [79]. The 24 h volume of bile was about 2100 mL and the total amount of bile salts about 37 g. Bile excretion (volume and bile salts) was minimum before the morning meal. The excretion of bile salts increased immediately after meal intake: within 2 h after the morning and afternoon meals, values were about 300% higher than those measured before the morning meal. This was the result of the excretion of a highly concentrated bile, while a marked increase of the volume excreted only occurred 2–3 h after the meal intake.

Extracorporeal derivation without a return of bile to the duodenum led to a 23% decrease of apparent energy digestibility and a 32% decrease in the total lipid apparent digestibility. This particular involvement of bile secretion in the digestion of lipids was first established by [35]. This was further supported by studying the responses of bile flow, biliary lipids and bile acid pool in the pig to quantitative variations in dietary fat [80]. A similar impact on the digestive utilisation of lipids was observed after the diversion of bile (restitution into the ileum instead of the duodenum): the apparent digestibility of lipids was strongly reduced (–60%) while an 81% decrease of the daily bile acid output was recorded [76, 77]. This evidenced the role of the pig small intestine in maintaining an efficient enterohepatic circulation of bile acids. The quantitative absorption of total bile acids was assessed by Legrand-Defretin et al. [117] who showed that the mean total bile acid concentration averaged 83.9 and 15.6 μM in portal and arterial blood respectively, and that 216.9 mmol of total bile acids were absorbed over 24 h. They described the time courses of blood concentration and absorption throughout the light-dark cycle, and hepatic uptake averaged 79.3%. While bile salts were formerly considered to be reabsorbed from the distal intestine, it was possible to show that, in the pig, the proximal intestine plays a very important role in recycling biliary salts [81].

Then, turning to a biomedical purpose, the pig was used as a model of gall-stone formation in humans and the group tried to develop cumbersome methods for purification and identification of the various constituents of bile possibly involved in the crystallisation of biliary cholesterol [82, 118]. A model was developed to induce cholesterolic lithiasis in the pig fed a diet enriched with cholesterol and cyclodextrine, while the beneficial effect of soy proteins was shown to result from a change in the bile acid pool leading to reduced hydrophobicity [22, 83]. However, this very interesting animal model is a separate issue, different from that of digestive physiology in pigs.

5. KINETICS OF DIGESTION: QUANTITATIVE AND QUALITATIVE APPROACH TO LUMINAL DIGESTA

Digestion is the overall result of the conjunction of several functions. Both the passage of digesta and the enzyme hydrolysis of substrates contribute to determining the rate of release and absorbability of nutrients. This led to developing several methods of obtaining digesta from the tract of conscious animals, and to investigate the qualitative and quantitative characteristics of digestive contents.

5.1. Gastric emptying

Gastric emptying has a key role as it determines the rate of food delivery to the duodenum. We tried to improve the overall knowledge of the mechanisms involved in the control of the flow, using both an original duodenal trans-thoracic reentrant fistulation technique and the modelling of emptying curves [105]. On this basis, we studied the differential emptying of the main constituents (starch, proteins) of a semi-purified diet [39, 40]. This allowed to specify their respective emptying rate and to give preliminary support to the assumption that the kinetics of starch-emptying determines the kinetics of appearance of absorbed sugars in the portal blood stream as described by Rérat [141, 146].

However, as the trans-thoracic reentrant fistulation was a cumbersome technique, we renewed the use of the old gastric fistulation technique, much easier to perform. It allows direct access to gastric contents for a differential estimate of emptying from gastric remnant measurement. The comparison of the estimations given by duodenal and gastric fistulations, respectively, showed differences. Gastric emptying of dry matter was steadier and more marked during a 7 h postprandial period when using gastric fistulation, and starch emptying was probably underestimated when measured in duodenal contents [41]. The question then arose as to whether the rate of gastric emptying was limiting intestinal carbohydrate absorption or not, suggesting that the rate of hydrolysis of the starch emptied from the stomach might also be the limiting factor. Similar studies using gastric fistulation in pigs fed cereal-based diets such as barley, wheat or maize, evidenced early differences in the kinetics of emptying [113, 114]. Within the first postprandial hours, wheat produced the largest quantities emptied and maize the lowest. Under these conditions we confirmed that gastric emptying was highly responsible for the rate of absorption of carbohydrate and amino acids from the small intestine. Nevertheless, it was not possible to determine with certainty whether the rate of gastric emptying was limiting intestinal carbohydrate absorption or not.

5.2. Kinetics of passage and apparent digestibility within the small intestine

To quantify the yield of digestion and absorption, it must be kept in mind that, in pigs, most nutrients are absorbed from the small intestine. It was thus of importance to quantify the losses of the various nutrients escaping absorption by crossing the ileocaecal junction. Despite severe anatomofunctional difficulties [107], we developed a specific ileocolic postvalve fistulation technique, avoiding any mixing of the intestinal digesta collected with the colonic contents [48]. The normal pattern of MMC controlling the passage of digesta along the small intestine was shown to be preserved [51, 52] despite the heavy procedures required for surgical preparation and postsurgical care, and provided that a normal colic repletion was maintained by returning digesta. While digesta were formerly collected from ileal T cannulae (i.e. too proximal) and pooled for 6- or 8-hour periods [21, 181], for the first time our ileocolic postvalve fistulation allowed to preserve the functional role of the ileocolic valve and to describe in details (collection every hour or 2 hours) the true kinetics of digesta passage from the small to the large intestine [52]. This also allowed to calculate a precaecal digestibility.

It was then possible to estimate the quantities of nitrogen (around 70 g unabsorbed proteins) and carbohydrates escaping absorption from the small intestine [53]. The dietary starch and protein sources were shown to induce different effects [54]: (i) the type of starch has a significant influence on the apparent nitrogen precaecal digestibility; (ii) the dietary protein source significantly influences the apparent digestion coefficient for dry matter and nitrogen; (iii) there is a significant interaction between the type of starch and the protein source as regards the apparent nitrogen digestibility. The systematic comparison of the precaecal and faecal digestion coefficients, for diets formulated as a factorial combination of 2 starches and 2 protein sources, showed that precaecal digestibility was much more [49]. Therefore, considering that the precaecal amino acid digestibility might be a better indicator of amino acid availability than the faecal one, we used the ileocolic postvalve fistulation technique, under different dietary protein sources, to determine the amino acid composition of digesta leaving the small intestine and to calculate the apparent digestibility of amino acids before any modification by colonic flora [55–57].

It was shown that nitrogen precaecal digestibility was not a good predictor of precaecal amino acid digestibility. This means that amino acid digestibility is in itself an insufficient criterion because of the dispersion of the values of each amino acid, especially some essential amino acids. We also evidenced that a rather repeatable amino acid hierarchy was found with very different diets. The faecal digestibilities of most amino acids exhibit a similar hierarchy, but large distorsions do exist depending on the activity of the caecocolic flora. This confirmed that faecal digestibility may lead to erroneous estimations, while precaecal apparent digestibility of aminoacids gives a good picture of true digestibility. However, this gave rise the question of the difficult evaluation of endogenous sources and their variability [55]. Looking at the total and free amino acid composition of digesta by multivariate analysis, to compare the composition of digesta to that of dietary proteins, and that of various endogenous proteins or digesta collected under a protein-free diet, it was shown that the influence of dietary protein was large, mainly during the postprandial hours, even for a highly digestible source of proteins [56]. We confirmed that the precaecal digestibility of amino acids was more adequate than the faecal digestibility, but the influence of the dietary protein source on the apparent and true digestibility of each individual amino acid was very important. The nature of starch significantly affected the apparent digestibility of most amino acids, but only the true digestibility of some of them, and the effect of a starch-protein interaction was significant in most cases [57].

5.3. Basis for a current estimation of amino acid availability

As the ileocolic postvalve fistulation technique was a cumbersome technique for research purposes only, we tried to develop a new technique suitable for the measurement of precaecal digestibility, in order to base the feed formulation: what is referred to as the ileorectal anastomosis technique [112]. Particularly in the view of measurement of dietary amino acid digestibility, this method was evaluated in comparison with ileocolic postvalve fistulation in the pig [58], as well as with other methods and animal models [63]. The fate of the colonic flora in the bypassed colon was also verified [61]. The ileorectal anastomosis technique was thus widely used in the pig, for example to assess associative effects between different fibre sources on the digestibilities of amino acids but also energy and cell wall components [115], and in piglets [19].

However, the digesta collection procedure may affect the estimate of precaecal digestibility [59], a fact that led to comparing different surgical variants of the technique (end-to-end vs. end-to-side anastomosis, with or without a preserved ileocolic valve) for both protein and plant cell wall digestion [116]. On the basis of the digestibility values of the NDF fraction, the end-to-side anastomosis procedures led to a stimulation of the fermentative processes generated by the remaining flora of the large intestine. This situation induced a significant increase and an overevaluation of the apparent digestibility of the fibrous components and amino acids. More appropriate was the end-to-end procedure which has been generalised in our conditions. This method was of tremendous importance in understanding the physico-chemical processes involved in the digestion of dietary proteins, their breakdown and the absorption of amino acids and peptides in the small intestine, in relation with the study of endogenous losses vs. the recycling of nitrogen (see below). Nutritional consequences on pig feeding and diet formulation are also expected in the very near future. Indeed the concept of ileal or precaecal digestible amino acids gained major importance in the explanation of protein efficiency and deposition in the pig [172].

6. KINETICS OF NUTRIENT ABSORPTION: QUANTITATIVE AND QUALITATIVE APPROACHES

The differences between the amounts of nutrients ingested and those excreted in the faeces do not completely account for the amounts appearing in the organism. The disappearance of a nutrient during its passage through the digestive tract does not always mean that it has been absorbed and does not indicate in which form it is liable to appear in the organism. This nutrient may be decomposed or destroyed in the gut as affected by the microflora; it may be metabolised by the cells of the gut wall during its absorption. It may be retained by the gut wall. Other nutrients, for instance certain amino acids, may appear, either vehicled by gastrointestinal secretions, or synthetised by microorganisms. Moreover, the kinetics of nutrient absorption has to be studied to understand the variations in the nutritive value of the feeds and especially that of protein, according to the "availability" of the nutrients they contain and to their more or less rapid absorption. Indeed, from a chronological point of view, the simultaneous arrival of all amino acids on the sites of protein synthesis seems to be required in order to obtain the best feed efficiency. A synchronous supply of energy also seems to be necessary.

6.1. A methodology for the assessment of absorption

A methodology was thereby developed, which was not based on the disappearance of nutrients from the gut lumen, but on their appearance in the fluids draining the digestive tract. Variations in the blood or lymph concentrations of a nutrient reflect the overall digestive processes to which the nutrient has been subjected, and its possible metabolisation in the gastrointestinal cell wall. A qualitative description of absorption can thus be made from the changes in intestinal lymph composition with time (lipids: [137]) or more generally from porto-arterial differences in nutrient concentrations indicating the degree of enrichment of the portal blood draining the whole gut, relative to the afferent arterial blood of the intestine (minerals: [69, 70]; amino acids issued from various proteins: [132, 135, 136]; sugars: [14–16, 149, 150]). A quantitative description of absorption can be made by measuring the blood flow rate in the portal vein (initially using an electromagnetic flowmeter) [140], while blood samples can be obtained by permanent catheterisations in the portal vein [3] and the carotid artery [141]. From the combination of these techniques, absorption is calculated according to the formula: $Q = (Cp - Ca) D \cdot dt$, where $(Cp - Ca)$ represents the porto-arterial differences in nutrient concentrations, D is the blood flow rate in the portal vein, and Q is the amount absorbed within the time interval dt [155]. However, as it does not account for metabolisation processes in the gut wall, this measurement only concerns apparent absorption.

6.2. Absorption of minerals, sugars and amino acids

Numerous original results were obtained by Rérat from 1970 to 2000 using the above mentioned methodology for the assessment of absorption. Let us just mention some of the most important contributions:

– The influence of the chemical form of phosphorous on its absorption rate, as aluminoferrous phosphate and wheat bran phosphorous are absorbed late in comparison with disodium phosphate; P accretion depends closely on the simultaneous presence of calcium [68–71].

– The slower absorption kinetics of total amino acids of some cereals (e.g. barley, corn) relative to what happens to other feeds (e.g. fishmeal, wheat) and the variable absorption rate of individual amino acids according to studied feedstuffs, as well as a differential absorption rate of hexoses and amino acids [65, 153, 154, 161, 163]. In contrast, the absorption rate of total and individual amino acids issued from purified proteins (rapeseed, casein) was faster than when issued from untreated feeds [65].

– The variable timing of the absorption of carbohydrate enzymic digestion products (e.g. high for cerelose and sucrose, medium for starch, slow for lactose) [157, 163].

– The large metabolic phenomena occurring in the digestive wall, resulting in the absorption of high amounts of lactic acid and the metabolisation of some non-essential amino acids e.g. uptake of glutamic acid and glutamine, synthesis of alanine [133, 134, 153, 161, 163, 167], and of some hexoses e.g. partial transformation of fructose issued from sucrose, and galactose issued from lactose, into glucose [151, 156, 157].

– The great influence of prehydrolysis procedures on the absorption rate of hexoses proceeding from disaccharides such as lactose. The use of hydrolysed lactose, more and more frequent in human foods (pastries...) may result in a too quick and large appearance of galactose in body fluids with potential long-term consequences on human health (cataracts...) [165].

– The extent to which the availability of nutrients may be modified by the technological processes undergone by feeds. For example, hydrogenated maltose is well hydrolysed in the gut, but its released sorbitol moietie is poorly absorbed [166]. In addition, lactose-lysine formed when using drastic milk-drying procedures is partly and slowly absorbed, but mostly excreted in urine [170].

– In vivo testing of the accuracy of an in vitro technique used to forecast amino acid availability [64].

– Incidentally, the measurements of oxygen consumption from porto-arterial differences allowed to evaluate energy expenditure due to the aerobic metabolism of the organs drained by the portal vein after meal intake (18% more than during fasting) [148].

7. INTEGRATIVE APPROACHES ON NUTRIENT HANDLING, STORAGE AND UTILISATION

7.1. Endogenous nitrogen recycling and digestive nitrogen fluxes

During digestion and interprandial periods, large amounts of endogenous products appear in the gut lumen, composed of secretions, intestinal desquamations, mucus and several substances coming from blood (albumine, urea, free amino acids). Knowledge of the amounts secreted, their variations and sources, and the amounts reabsorbed is interesting for the determination of their share in the nitrogen requirements. Feeding animals with a protein-free diet during a long time does not significantly modify the composition and efficiency of exocrine pancreatic secretion, which is a very important fraction of endogenous nitrogen [37]. Such diets were used to measure endogenous nitrogen recycling. The amounts of free amino acids appearing in the portal vein (2 $g \cdot h^{-1}$) after protein-free diet intake and their pattern were thus analysed [164].

The combination of the various techniques respectively developed to study digestion, absorption, and secretions, together with the availability of stable isotopes (^{15}N), opened the way for the study of endogenous nitrogen fluxes in the digestive tract [177], providing a first estimation of 85% for the recycling of endogenous amino acid supplies (i.e. 46 g out of 54 g produced). The composition of various endogenous and microbial proteins (meconium of piglet small intestine and colon, axenic piglet faeces, bacteria isolated from faeces under different dietary conditions) were described [111], as well as that of pancreatic secretion [28]. The contributions of nitrogen from exocrine pancreatic secretion and bile to nitrogen fluxes were assessed [38]. The ileal and faecal digestibilities of amino acids were revisited in pigs with ileocolic postvalve fistulation and fed a casein diet, taking into consideration the exogenous vs. endogenous origin of nitrogen. In these conditions, the reabsorption of endogenous nitrogen amounted to 79% up to the end of the small intestine and to 88% over the whole digestive tract [60, 178]. Ileal endogenous losses of amino acids, which depend on the level of protein and the presence of ANFs, were then evaluated in piglets with ileorectal anastomosis in association with the use of isotope dilution performed either with labelled animals or with labelled diets [75]. In both cases, the ileal endogenous losses of nitrogen and amino acids were higher than the basal losses determined with a protein-free diet. The method was sensitive enough to evidence significant differences between two pea cultivars in terms of phenylalanine and leucine when measured with labelled diets.

Among the sources of endogenous nitrogen, urea was particularly studied. Its fluxes in the body are controlled by simple physical diffusion laws. Being thus secreted into the digestive lumen, this nitrogen metabolism end-product may be used by intestinal microorganisms for synthetising microbial proteins found in faeces. The balance between the amounts of urea secreted into the gut lumen and the absorbed amounts of ammonia, a metabolic microbial waste product, was measured in various feeding conditions [142, 147, 152].

7.2. Respective roles of enzymatic and microbial hydrolysis in digestion

The role of each digestive organ in digestion may be evaluated by suppressing its secretion, which is only possible for organs with an excretory duct. In the case of the pancreas, the derivation of the Wirsung duct resulted in a depression of nutrient absorption, very important for glucose (85%), and less important for amino acids (50%), but the composition of the free amino acid mixture absorbed was only slightly modified [169]. "Normal" digestion was reestablished when the pancreatic juice was reinjected into the gut lumen. Maldigestion of feeds and malabsorption of nutrients result in the formation of undigested substances liable to be hydrolysed by large intestine microflora.

Microbial metabolism in the large intestine was appreciated by measuring the production and absorption of volatile fatty acids [159], and of ammonia from urea and undigested proteins. An available form of phosphorous is produced by bacteria from undigestible phytic phosphorous [72]. Volatile fatty acids are the main products of the digestive flora in the large bowel, allowing a large recovery of energy from nutrients poorly broken down in the small intestine. From several experiments with different energetic [67, 128, 160, 168], it was possible to show that the production and absorption of volatile fatty acids increased more or less with the crude fibre content of the feed, according to its nature, and with the presence of some indigestible carbohydrates such as lactose or sorbitol in the diet. Contrasting with the early energy absorption derived from enzymic degradation, energy absorption under the form of volatile fatty acids occurred later, thus making it possible to partially bridge the energy gap during the interprandial period [145].

7.3. Hepatic handling of absorbed nutrients

An extent of the Rérat methodology [176] allowed to study the kinetics of the disposal of nutrients by the liver, by simultaneously using the cannulation of a hepatic vein (liver blood output) and an electromagnetic probe around the hepatic artery. Thus the most interesting features concern the influence of absorption kinetics on the ability of organs such as the liver or the peripheral tissues to store and release nutrients and the utilisation of dynamic aspects in the analysis of the role played by the "time" factor in protein tissue metabolism. This methodology enabled to study the digestion of some carbohydrates [167], proteins [175] and medium-chain triglycerides [73, 74] in relation with hepatic metabolism and with peripheral tissue metabolism, according to their technological pretreatment (enzyme prehydrolysis...).

To study the relationships between absorption kinetics of nutrients, their storage in the liver and their peripheral tissue utilisation, diets containing several levels of purified proteins, e.g. casein or rapeseed, were used [175] or nutrient solutions were infused into the duodenum [162, 167]. The purpose of the latter experiments was to study the influence of the physico-chemical structure of administered nitrogenous substances (oligopeptides – issued from mild enzymic hydrolysis of milk proteins – vs. free amino acids with the same pattern) on absorption and metabolism. It is known that these two groups of substances are released into the gut lumen during enzymic digestion of proteins in various proportions, and absorbed by the enterocyte via transport systems differing from one group to another. During their transport, oligopeptides are hydrolysed into their constituent amino acids by the enterocyte so that only free amino acids appear in the portal vein. The fact that oligopeptides use specific transport systems might minimise the competition for transport sites and make their absorption globally more efficient. It was thus interesting to determine the influence of each partner present in the intestinal lumen – free amino acids vs. oligopeptides – on the kinetics of appearance and distribution of free amino acids in the "milieu intérieur", liver and peripheral tissues. This was important for a better knowledge of the transport mechanisms in the gut wall, but also for applied reasons in human enteral nutrition (humans with short bowel syndrome).

After meal intake, the techniques developed [176] allowed to assess the amounts of nutrients appearing in the blood, their composition and changes with time, as well as the kinetics of their uptake and release by the liver, and, by contrast, by the peripheral tissues. Furthermore, these techniques enabled us to appreciate the endocrine reactions of the gastroenterohepatic axis involved in the regulation of absorption and metabolism. Under these conditions, the appearance of amino acids in the portal blood was greater, more rapid and more homogeneous after duodenal infusion of an oligopeptide solution than after that of free amino acids, irrespective of the amount of the infusate. The coefficient of absorption of most individual amino acids was higher after the infusion of oligopeptides than after that of free amino acids, with the notable exception of methionine for which the opposite was true [160]. These differences between the two infusates were lowered when an available carbohydrate was present in the solution, but nevertheless remained significant for the first hour after the infusion [143, 144, 167]. Hourly insulin and glucagon production were highly correlated with the appearance of amino acids in the portal vein. The long-term (8 h) uptake of free amino acids into the liver and peripheral tissues differed in pattern according to the nature of the duodenal infusion. Peripheral uptake was appreciably less well balanced after infusion of free amino acids (deficiency of threonine and phenylalanine) than after infusion of small peptides (methionine deficiency) [167]. It thus appeared that the absorption kinetics which results in important variations in the temporal distribution of free amino acids in the tissues may be at the root of transitory imbalances in tissue amino acid uptake, and, as a result, of a lower nutritive value. This concept has now been updated under the form of "slow proteins" vs. "fast proteins".

8. INTEGRATIVE APPROACHES: NEUROHUMORAL REGULATIONS AND ADAPTATIONS

Initial observations concerning the control of gastric emptying [6, 105] suggested the prominent role of nervous reflexes in the regulation of passage of digesta. Later on, several regulatory peptides such as motilin, cholecystokinin, secretin, pancreatic polypeptide, neurotensin, etc., were also shown to play an important role in the control of gastrointestinal motility [42, 43] and digestive secretions [45, 46, 85, 86, 120]. Moreover, Rérat et al. [158] showed that an increase in the level of proteins in the diet induced large changes in the hormonal production of the splanchnic area, with generally large parallel increases of gastrin and glucagon, and to a smaller extent, of somatostatin, gastro-inhibitory peptide and pancreatic polypeptide. The highest production of insulin was found for a well-balanced mixture of proteins and sugars. The consequences of such phenomena for the regulation of digestive functions and nutrient metabolic utilisation are of utmost importance. However, two main aspects have to be considered: the regulation of the functions (food intake, food passage, luminal hydrolysis, absorption and metabolism), and the adaptation of the functions to the composition of the diet or to modifications in digestive ability. Our group thus participated in the growing knowledge of the integrated neurohumoral control of nutritional functions. Some points have previously been mentioned and, in the present section, we shall only develop aspects concerning the control of food intake in the pig, the role of afferences from the digestive tract, and the consequences of a small intestine resection.

8.1. Central and peripheral control of food intake and digestive functions

The feeding behaviour of the pig was studied by Auffray et al. [7] who showed that the daily number of spontaneously consumed meals is very high in the young animal (around 20) and then decreases fast after weaning, reaching the "adult" number (3 or 4 meals) at puberty. These meals are distributed all over the 24-h cycle, except for a period of 4 h at dawn. Several mechanisms take part in the control of the pattern and quantity of food eaten. Humoral metabolic signals are probably involved, either directly or indirectly, but were not thoroughly investigated, except for the "ileal brake" mechanism (inhibitory influence on gastric motility) probably mediated through a peptidergic pathway originating from the presence of volatile fatty acids in the ileum [47]. However, most of the work was related to either central or peripheral nervous influences.

To approach the role of the central nervous system, an attempt was made to determine whether the pig, like other mammals, possesses regulatory centres of appetite in the hypothalamus. These centres were evidenced and, owing to the preliminary attempt to establish a stereotaxic atlas of this area of the brain, it was possible to assay the destruction or the stimulation of these centres [5]. Thus the destruction of the "centre of satiety" led to the production of severely hyperphagic obese animals. Beyond these particular initial studies, it appeared necessary to improve the available knowledge of the pig brain. This led the neurobiology group of Laplace to initiate, as from 1986, the preparation of a specific stereotaxic atlas of the whole brain [62]. To secure the technical conditions of this intricate work and to allow an accurate approach to the integrative processes occurring in various central nervous structures, a specific stereotaxic technique was developed for the pig [126] and preliminary studies were conducted with magnetic resonance imaging [127].

In parallel, we considered that the brain probably participates in, and needs to be informed about, the functioning of the digestive tract. This led us to pay particular attention to the role of the peripheral nervous system and mainly to the role of the vagus nerve. This 10th cranial nerve includes both efferent fibres whose cell bodies are located in the brain stem, and many afferent sensory fibres whose neuronic somas are located on its cervical route in the nodose ganglion. Histological and immunocytochemical studies revealed the presence of neuropeptides such as galanin in these vagal sensory neurons [131], but we tried to evaluate the functional importance of the vagal afferent firing from visceral receptors, considered as an essential input to the brain, in conscious pigs. For this purpose an original surgical technique for selective vagal deafferentation (interruption of the vagal afferent pathways from the digestive tract to the brain stem) was developed, either partial [50] or total [99]. It allowed us to evidence the importance and general significance of sensory afferent information.

The gastroduodenal area appeared as the origin of numerous afferent messages which can contribute to the control of food intake, gastric emptying, pancreatic function, etc. For example, gastric emptying was strongly affected [109] as total vagal deafferentation results in a severe retention of gastric contents. It was established that retention results from the loss of all afferences, while the concomitant reduced volume of efferences is of little importance. During the past few years, the particular importance of the mechanisms responsible for pylorus function [122, 124] and the role of gastric fundus distension in relation with the short-term control of food intake [119] further supported the prominent role of visceral sensitivity. The vagal deafferentation also induced significant changes in the pancreas which exhibited significant reductions in the pancreatic tissue mass and in the various enzyme activities, thus suggesting the importance of intestinal sensitivity for the pancreas [110].

8.2. Adaptation after enterectomy and restoration of digestive ability

The wide knowledge collected on digestive function in relation to pig production was further extended to biomedical research, using the pig as a model, originally under the authority of Prof. J. Hamburger. This first step was aimed at using the excretory capacity of small bowel loops in the case of kidney failure [84]. It did not appear to be possible to ensure a sufficient excretion of uric acid and creatinine. However, several points called for attention to the question of intestinal adaptation after either small intestine resection or bypasses whose consequences on somatic and visceral growth were studied under various conditions [90, 95]. The observed characteristics of the somatic and intestinal adaptation, and the differences recorded between the effects of resection and bypasses, led us to hypothetise that some neurohumoral relationships might support the restoration of an adequate proportion between overall digestive ability and body size and its nutrient requirements [91, 92].

In order to explore the humoral mechanisms possibly involved in compensatory hypertrophy, we developed a long-term cross-circulation technique between conscious pigs paired by identical blood group and histocompatibility [88]. Continuous blood cross-circulation was maintained for 410 h either between normal pigs or between a normal and a 30% jejunectomised pig. Both the jejunectomised pigs and their unoperated partners showed a significant hypertrophy of the small intestine, whether residual or intact, as compared to intact pigs cross-circulated between themselves. It was thus possible to demonstrate the involvement of a blood-borne factor responsible for compensatory hypertrophy [100].

In view of these results, our hypothesis was that compensatory hypertrophy of the residual small intestine after partial enterectomy might be mediated through a neurohumoral feedback whose efferent pathway was the evidenced blood-borne factor, and whose afferent pathway might be the vagal sensory pathway. This was confirmed as it was shown that compensatory mucosal hypertrophy after small bowel resection was severely impaired by vagal deafferentation [101, 102]. This suggested that, besides intrinsic control factors of epithelial renewal, the visceral sensitivity supported by vagal afferences might be a determinant of true adaptation as a result of the homeostatic control of functional digestive ability.

9. CONCLUSION

Great progress has been made over the 40 last years in the field of animal production in general and in pig production in particular. In the worldwide circle of pig research, France had a prominent role due to a simultaneous involvement in animal production and in animal physiology. This review has been written as an homage to the scientific productivity of the group set up forty years ago in Jouy-en-Josas to deal with the simple but fundamental concept that a better understanding of pig digestive physiology might improve the management of pig nutrition, to solve current problems of the pig industry and anticipate its further needs. Therefore, this paper aims at providing a valuable overview of the highly original contribution of our group to the complex scientific field of regulatory physiology of the digestive tract function in the pig.

The simultaneously growing knowledge of the gastrointestinal motility and food passage, and of the digestive secretions allowed us to lighten the digestion of feed within the lumen. The qualitative and quantitative approach of nutrient absorption was a focal point. Absorption is indeed related to what happens in the tract, leading to question the epithelial function, the metabolism within the intestinal wall, and the recycling processes. It is also related to the metabolism of the whole body tissues. Therefore we explored several key mechanisms taking part in the carbohydrate and protein handling by the digestive tract and the liver.

Owing to our knowledge of both digestion processes and gut functioning we contributed to the pioneering work on amino acid availability through ileal digestibility measurements. Attention has been paid to the practical impact of this knowledge in terms of feedstuffs characterisation and of endogenous supplies. Moreover, the addition of endogenous protein to the digesta not only raises the question of the efficiency of dietary protein digestion. It also interferes with the quantification of the real availability of amino acids from the diet, and the evaluation of the net requirement for available amino acids, presumably as an important part of maintenance needs [172]. This is of great interest in the context of pig production because it allows a better adjustment of the supplies to the requirement and a reduction of nitrogen pollution.

When looking for the future, some interesting ways have been identified which require further exploration with updated methods and new techniques. We need much additional research concerning adaptations to understand the underlying neurohormonal mechanisms within the whole body inter-organ regulations, as well as the nutrient-induced and gene-related changes. A wide and exciting field has been opened concerning the role of the enteric nervous system and the afferent information from the digestive tract to the brain, as related to both the food intake control and the integrated control of the digestive tract function. Next step will involve some of the techniques we developed as well as new techniques related to functional imaging and molecular biology. We hope this paper will initiate wider benefit for the future, giving opportunities for further progress within the new era of post-genomics and integrative physiology.

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