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Dietary influences on the secretion into and degradation of mucin in the digestive tract of monogastric animals and humans

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ABSTRACT

Current information on the effect of diet on the secretion of mucus and the recovery of mucin in ileal digesta is summarized. A general description of mucus structure and its degradation in the small and large intestine is provided. As the protective lining of the entire gastrointestinal tract, mucus gels are exposed to all chemical and physical forces of digestion. Most important among these is the proteolytic breakdown of mucus gels into component mucin subunits and their subsequent release into the intestinal lumen. Erosion of mucus gels is countered by synthesis and secretion from the underlying epithelium. Diets can influence this process, both indirectly by their effects on digestive processes most importantly with respect to the amount and distribution of proteolytic enzymes in the intestinal lumen, and directly by the physical forces which they exert on the gastrointestinal mucosa. Adaptive changes in goblet cell activity have been noted in response to different diets. Once in the intestinal lumen, little further degradation of mucus occurs prior to the large intestine. Once in the large intestine mucin is fermented by resident microbial populations. The recovery of undegraded mucin in ileal digesta has important implications for nutritional studies: firstly because it may represent a considerable loss of endogenous amino acids and carbohydrates and secondly because it may provide insight into the effects of diets on the digestive tract itself.

KEY WORDS: mucin, ileal digesta, secretion, endogenous protein, pigs

INTRODUCTION

Mucus is a large molecular weight glycoprotein that covers the entire lumenal surface of the gastrointestinal tract. Several functions, primarily related to the protection of the underlying epithelium, have been attributed to the mucus layer (Neu-

tra and Forstner, 1987; Turnberg, 1987; Lamont, 1992). Mucus, together with bicarbonate, protects the epithelium from vigorous digestive processes and corrosive gastric juices by creating an unstirred layer and by acting as a diffusion barrier, preventing large molecular weight compounds (such as proteolytic enzymes) from reaching the epithelium. Mucus traps toxins and bacteria preventing infection. Adherent mucus, along with soluble mucus in the intestinal lumen, acts as a lubricant providing protection from mechanical damage caused by the passage of food. In addition, mucus also plays an important role in the digestive processes by creating a digestive zone in which enzymes are immobilized near the epithelial surface, preventing their rapid removal by peristalsis and placing them in a more favourable position for digestion. As such, mucus is exposed to all chemical and physical forces of digestion. Allen (1981) proposed that proteolysis, augmented by physical abrasion, is the primary reason for the presence of mucus in the lumen of the digestive tract. In addition, evidence suggests that, once in the intestinal lumen, little degradation of mucus occurs prior to the large intestine where it is fermented by enteric bacteria (Hoskins, 1984). The recovery of undegraded mucin in ileal digesta has generated a great deal of interest from a nutritional point of view since it could represent a considerable proportion of endogenous protein and carbohydrate recovered at the distal ileum.

Endogenous protein originates from digestive enzymes (salivary, pancreatic and mucosal), gastric, intestinal and bile secretions, and sloughed epithelial cells. Many reviews on endogenous protein can be found in the literature (e.g., Low, 1982a; Souffrant, 1991; Nyachoti et al., 1997). Endogenous nitrogen derived from gastrointestinal mucosa is particularly important since it is estimated to represent 64 to 83% of the total daily amount of endogenous nitrogen entering the lumen of the digestive tract (Low, 1982a; Souffrant, 1991). This observation is consistent with the high metabolic activity of the mucosa. Approximately 43% of whole body protein synthesis occurs in the liver and gastrointestinal tract, despite the fact that these organs represent only 14% of whole body protein (McNurlan and Garlick, 1980). Consistent with its secretory role, the rates of protein synthesis in mucosa are twice that in serosa (Garlick et al., 1980; Attaix and Arnal, 1987). While McNurlan et al. (1979) suggested that as much as 50% of protein synthesized in jejunal mucosa might be attributed to replacement of lost epithelial cells, DaCosta et al. (1971) reported that only 8 to 15% of protein lost from the small intestine was derived from this source. In addition, while 70 to 80% of endogenous nitrogen is estimated to be reabsorbed (Low, 1982a; Souffrant et al., 1986; Krawielitzki et al., 1990), little digestion of mucin occurs prior to the large intestine (Hoskins, 1984). These data, which are supported by observations from digestibility trials, point to mucin as an important source of endogenous protein. The presence of mucin in ileal digesta, because of its high threonine, serine and proline contents (Scawen and Allen, 1977; Mantle and Allen, 1981), has often been implicated in

the predominance of these amino acids in endogenous protein (e.g., Sauer et al., 1977) and thus their relatively low apparent ileal digestibilities in diets for pigs which is often reported in the literature (Sauer and Ozimek, 1986). In addition, fermentation of mucin by bacteria in the large intestine would explain the considerably large intestinal disappearance of these amino acids, particularly threonine (Sauer and Ozimek, 1986).

The objective of this review is to present current knowledge regarding the effects of diets and dietary ingredients on the secretion of mucus from the gastrointestinal mucosa and its subsequent recovery in ileal digesta and faeces. For more comprehensive discussions of mucus structure, function and physiology, readers are directed to several previous reviews (Allen, 1981, 1984; Allen et al., 1984, 1993; Forstner and Forstner, 1986; Neutra and Forstner, 1987; Mantle and Allen, 1989; Lamont, 1992).

STRUCTURE OF MUCUS

Adherent mucus gels are comprised of large molecular weight glycoproteins, 2×10^6 daltons, called mucins. Mucins consist of four subunits, weighing approximately 5×10^5 daltons each, that are linked by disulphide bonding and are arranged into the 3-dimensional polymeric structure necessary for gel formation. Mercaptoethanol- or proteolytically-reduced glycoprotein subunits lack gel-forming properties (Allen et al., 1984; Bell et al., 1985; Pearson et al., 1986). Two different models have been proposed for the polymeric structure of mucin. Allen et al. (1981) proposed a four bladed windmill structure in which the protein backbones of all four mucin subunits are linked in a common nonglycosylated region. Carlstedt and Sheehan (1984) proposed that mucin resembles a 'coiled thread': a long peptide containing several glycosylated and nonglycosylated regions. Mucin polymers overlap and are joined noncovalently to provide the structural basis of the gel. These noncovalent interactions are strong enough to resist osmotic pressure and solubilization, but not strong enough to resist gel spreading or mechanical disruption (Bell et al., 1985). Mucus gels are filled with large volumes of water, up to 95% by weight, and organic constituents such as lipids, proteins, ions, and enzymes that are probably acquired from epithelial secretions and exfoliated and disrupted cells (Neutra and Forstner, 1987). Contaminant materials, including lipids and proteins, strengthen mucus gels making these more resistant to proteolysis (Slomiany et al., 1984; Lee et al., 1987; Sellers et al., 1991).

Mucins are characterized by high carbohydrate, typically over 80% of dry weight, and relatively low protein, 15 to 20%, contents (Table 1). The protein backbone of mucins is surrounded by oligosaccharide chains and resembles a 'bottle-brush' structure (Allen, 1981). The protein core is divided into at least two distinct re-

gions. The glycosylated region of the mucin molecule, representing more than 95% of the glycoprotein, is termed „native" mucin. Protein in this region accounts for approximately 65% of the total protein of mucin and is rich in serine, threonine and proline, which make up 40 to 70 mol/100mol of the native mucin amino acids (Table 1). Threonine and serine provide attachment sites for the oligosaccharide chains while proline may play a role in maintaining a particular conformation in the protein core, allowing carbohydrate chains to be packed very closely (Forstner and Forstner, 1986). It was suggested that in pig gastric mucin one in every three or four amino acids carry a carbohydrate chain (Allen, 1981). The tight packing of oligosaccharides makes this region relatively resistant to proteolytic attack. The second region, based on its accessibility to proteolytic attack, is the nonglycosylated or „naked" region, which represents about 35% of mucin protein or 4 to 5% of the total glycoprotein. This region has an amino acid composition similar to that of

TABLE 1

The composition of native and pronase-digested gastric and small intestinal mucins from pigs

	Gastric			Intestinal			Crude
	Native[z]	Pronase[z]		Native[x]	Pronase[w]		Mucin[u]
Composition, % DM							
carbohydrate	78.0	82.1		54.1	63.6		
protein	15.4	11.4		21.2	15.1		
sialic acid	2.9	2.9		21.6	17.5		
sulphate	3.7	3.7		3.1	3.8		
Amino acid composition, mol/100 mol							
threonine	18.3	25.3		27.2	34.8		15.7
serine	18.1	26.1		12.1	15.5		12.0
proline	16.0	18.5		16.4	21.0		12.5
remainder	47.6	30.1		44.3	28.7		59.8
Carbohydrate composition, mol/100 mol							
fucose	17.4	16.9	15.5[y]	9.6	14.0	10.5[v]	14.7
galactose	39.9	40.2	36.1[y]	26.5	29.5	27.6[v]	29.9
GlcNAc	29.9	29.1	35.3[y]	22.6	19.6	28.9[v]	24.4
GalNAc	12.8	13.8	13.1[y]	41.3	36.9	32.9[v]	31.0
GlcNAc/GalNAc ratio	2.3	2.1	2.7	0.6	0.5	0.9	0.8

[z] Scawen and Allen (1977)
[y] Stanley et al. (1983)
[x] Mantle and Allen (1981)
[w] Mantle et al. (1981)
[v] Choi et al. (1991)
[u] Lien et al. (1997)

an average globular protein, but is particularly enriched in cysteine, consistent with its role in the formation of the polymeric structure of mucus *via* the joining of mucin subunits by disulphide bridges. A third region, the link region, has also been identified (Neutra and Forstner, 1987; Mantle and Allen, 1989).

The carbohydrate fraction consists of galactose, fucose, N-acetylgalactosamine (GalNAc), N-acetylglucosamine (GlcNAc) and sialic acid. These are arranged into linear or branched oligosaccharide chains, varying in length from two to twenty-two sugars and are always linked (O-glycosidically) *via* GalNAc to the hydroxyl group of either serine or threonine in the protein core. Chain elongation occurs by alternating GlcNAc and galactose. In gastric mucin, chain elongation from GalNAc begins with galactose whereas in the small intestine it starts with GlcNAc. Branches develop by glycosidic bonding of GlcNAc to either galactose or core GalNAc. Sialic acid and fucose are always found in the terminal position at the nonreducing ends of main or branched chains. The arrangement of terminal oligosaccharides specify the ABH antigens of the ABO blood group system. Chains ending in GalNAc are type A, those ending in galactose type B and those terminating in fucose α1-2 galactose type H. Acidity of mucin glycoproteins are conferred by sialic acid, approximately 2 and 18% in gastric and intestinal mucin, respectively, and sulphate, 3 to 5% of the glycoprotein. Gastric mucins have longer carbohydrate chains than intestinal mucins, approximately 19 compared to 8 carbohydrate residues per chain. As a result, gastric mucins have a higher carbohydrate content and the two mucins differ markedly in carbohydrate composition. In pigs, gastric mucins have higher galactose and GlcNAc and lower GalNAc contents (Table 1). In humans, these differences are not so obvious (Table 2). In addition to these gross differences, there are also differences based on charge (e.g., Stanley et al., 1983; Wesley et al., 1983) and regional differences in composition within each of the areas of the gastrointestinal tract (e.g.,

TABLE 2

Selective carbohydrate composition (mol/100mol) of human gastric and intestinal mucins presented by blood group and the composition of mucin carbohydrate in ileal effluent

	Gastric[z]			Intestinal[y]		Ileal effluent[x]
	A	O	B	A	H	
Fucose	25.6	24.5	22.1	25.5	29.6	17.7
Galactose	34.5	37.2	40.3	24.3	31.8	38.9
GlcNAc	25.9	27.9	26.6	24.0	26.5	33.1
GalNAc	14.1	10.4	11.0	26.2	12.1	10.2
GlcNAc/GalNAc ratio	1.8	2.7	2.4	0.9	2.2	3.2

[z] Schrager and Oats (1974), determined by blood group specificity

[y] Mantle et al. (1984), determined by blood group specificity

[x] Lien et al. (1996)

Ohara et al., 1993; Karlsson et al., 1997; Nordman et al., 1997, 1998). As well, the extent of completeness of the oligosaccharide chains and the number of chains per molecule vary (Allen, 1981, 1984).

DEGRADATION OF MUCUS IN THE STOMACH AND SMALL INTESTINE

The mucus gel is not static, it is a dynamic balance between erosion and secretion. Several *in vitro* studies have demonstrated the proteolytic digestion of mucin into component subunits by pepsin, pronase, papain and trypsin (Scawen et al., 1977; Pearson et al., 1980; Mantle et al., 1981; Laszewicz et al., 1985; Lee et al., 1987). Similar results were obtained in *in vivo* studies. Allen et al. (1980) investigated the effects of peptic digestion of mucus by analyzing the relative amounts of pepsin-degraded (low molecular weight subunits) and native mucin glycoprotein in human gastric washouts. While 68 and 73% of mucin in the washouts, following stimulation by pentagastrin and insulin, repectively, were degraded, mucin obtained by scraping the mucosa of gastrectomy patients was degraded by only 21.2%. Mucus acquired by scraping the stomach and intestine of gastric and duodenal ulcer patients contained high amounts of degraded glycoprotein, 65.1 and 50.2%, respectively, compared to 33.4% in pancreatoduodenectomy patients, although there were no differences in the total amount of glycoprotein between the three groups (Younan et al., 1982). Sellers et al. (1989) demonstrated a correlation between the extent of polymerization of mucins and the strength and stability of mucus gels. Allen et al. (1990) illustrated this relationship in the context of the mucus gel in ulceration, indicating that proteolytic degradation weakens mucus gels, making these more susceptible to the physical forces of digestion. The introduction of pepsin into the stomach of rats caused a linear increase in the recovery of mucin up to a pepsin concentration of 1 mg/mL (Munster et al., 1987). There were no differences in mucin outputs as the pepsin concentration was increased from 1 to 2 mg/mL. Addition of a 10-fold excess of bovine serum albumin to the stomach resulted in a 60% reduction in the effect of pepsin on glycoprotein recovery (Munster et al., 1987). Furthermore, peptic degradation of mucus is reduced in the presence of ethanol, a pepsin denaturant (Laszewicz et al., 1985). Incubation of radioactive- labeled intestinal mucus glycoprotein in the upper and lower small intestine for up to 3 h resulted in a decrease in viscosity as degradation to mucin subunits took place (Ofosu et al., 1978). In that study, the recovery of the label was 70 to 90% suggesting that little absorption of degradation products occurred. Similar results were obtained for pancreatectomized rats leading these authors to suggest that limited degradation of mucus by epithelial enzymes might be a mechanism by which local control over the thickness of the mucus layer could be achieved. Bandurko et al. (1984) proposed that degradation of adherent mucus is necessary

to facilitate the transport of materials through the gel layer. In the absence of pancreatic proteases there is a reduction in the turnover rate of many large molecular weight proteins of the intestinal brush border (Alpers, 1984), further demonstrating a role for lumenal proteases in regulating mucosal protein synthesis.

Increased pepsin concentration is positively correlated with glycoprotein output (Allen et al., 1980; Munster et al., 1987) and the amount of degraded subunits (Allen et al., 1980; Laszewicz et al., 1985). It is, therefore, proposed that proteolytic enzymes continuously erode mucus gels throughout the gastrointestinal tract. Proteolysis is associated with a loss of amino acids (20 to 30%), except for threonine, serine and proline, and little (< 1%) or no loss of carbohydrate (Table 1). Total recovery of mucin is greater than 95%. Exhaustive proteolysis is without further effect (Mantle et al., 1981; Lee et al., 1987). The oligosaccharide chains, therefore, protect the protein of native mucin making it resistant to further proteolysis until their removal. According to Hoskins (1981) and Variyam and Hoskins (1983) at least 50% of the carbohydrates must be removed before any degradation of native protein occurs. The carbohydrate composition of mucin in ileal effluent from ileostomates suggests that some degradation of mucin oligosaccharide chains occurs prior to the large intestine (Lien et al., 1997). Compared to mucins obtained from either the stomach or small intestine, mucin in ileal effluent have lower fucose (17.7 vs 22.1 to 29.6 mol%) and higher GlcNAc (33.1 vs 24.0 to 27.9 mol%) contents (Table 2). Alternatively, these differences could result from incomplete synthesis of oligosaccharide chains as a result of increased mucin secretion (Forstner et al., 1984; Ohara et al., 1984). Forstner et al. (1984) noted an increase in the proportions of galactose and GlcNAc, at the expense of fucose and GalNAc, concomitant with a five- to eight-fold increase in mucin secretion from rat small intestinal rings exposed to cholera toxins for up to 4 h. These data support the proposition that at elevated levels of mucus synthesis, mucin oligosaccharide chain elongation may be incomplete, with mucin secreted in an immature state (Allen, 1981, 1984; Forstner et al., 1984). Terminal sugars would be most affected resulting in lower contents of fucose, galactose and GalNAc. The composition of mucin carbohydrates in ileal effluent (Table 2) is, however, within the range of values reported by Westley et al. (1983). Neither bile (Allen et al., 1984; Bell et al., 1985) nor luminal acid (Bell et al., 1985) appear to affect mucus degradation. It is assumed, therefore, that mucin subunits are largely undigested until they reach the large intestine (Variyam and Hoskins, 1983; Hoskins, 1984; Forstner and Forstner, 1986).

Mucin in ileal effluent is expected to consist of a mixture of gastric and intestinal mucins. The relative proportions from these sources will be determined by the type of diet consumed. Mucin in ileal digesta from pigs fed a protein-free diet was derived largely (approximately 75%) from the small intestine (Lien et al., 1997) while gastric and intestinal mucin were present in similar amounts (45 to 50% gastric mucin) in ileal digesta from pigs fed a wheat diet without or with

added pea fibre (Lien, 1995). Feeding bean-containing diets resulted in a much higher contribution of gastric to total mucin in ileal digesta compared to pigs fed pea- or lentil-containing diets (89.4 vs 47.6 to 54.9%; Table 3) (Lien and Sauer, 2000). In addition, mucin in ileal digesta is of low solubility, 20 to 40% (Clamp and Gough, 1991; Lien, 1995; Lien et al., 1997). The solubility of mucin is influenced, among other factors, by bile (Allen et al., 1984; Bell et al., 1985) and luminal pH (Bell et al., 1985). Furthermore, the protein status of the animal, probably *via* an effect on proteolysis of mucin (the breakdown of mucin to its component subunits increases the solubility of mucin), may also influence the solubility of mucin in ileal digesta. Soluble mucin was 24% higher in amino acid- compared to saline-infused pigs fed a protein-free diet, while total mucin output was only 6% higher (Lien et al., 1997).

TABLE 3

Ileal and faecal amino sugar recoveries and ileal mucin recovery in pigs fed barley or barley-legume diets[z], g/d

	Barley	Barley-SS7 peas	Barley-field peas	Barley-lentils	Barley-beans	SEM
Ileal amino sugars						
N-acetylgalactosamine	1.12[b]	1.51[a]	1.17[b]	1.21[b]	1.56[a]	0.069
N-acetylglucosamine	2.06[c]	2.64[b]	2.04[c]	2.21[c]	4.17[a]	0.106
Ileal mucin[y]						
total	7.77[c]	9.70[b]	7.15[c]	7.42[c]	14.01[a]	0.478
gastric	4.94[b]	5.33[b]	3.40[c]	3.64[c]	12.53[a]	0.396
intestinal	2.83[b]	4.37[a]	3.75[a]	3.78[a]	1.48[c]	0.135
Faecal amino sugars						
N-acetylgalactosamine	0.43[c]	0.52[bc]	0.50[bc]	0.60[b]	0.69[a]	0.026
N-acetylglucosamine	0.84[b]	1.04[b]	0.97[b]	0.99[b]	1.52[a]	0.051

[z] Lien and Sauer (2000)

[y] estimated from the GlcNAc/GalNAc ratio in crude mucin and the daily output of GalNAc in ileal digesta according to procedures outlined by Lien et al. (1997). All mucin in ileal digesta was assumed to be undegraded (native mucin)

[a-c] means in the same row with different superscript letters differ ($P<0.05$)

DEGRADATION OF MUCIN IN THE LARGE INTESTINE

The degradation of mucin occurs largely by bacterial fermentation in the large intestine (Hoskins, 1984). Clamp and Gough (1991) reported that, while glycoprotein represented about 15% of dry matter in ileostomy effluent, only traces were

found in faeces. Analysis of the lumenal contents of the ileum and large intestine of humans revealed differences in mucin constituents indicative of microbial fermentation in the large intestine (Vercellotti et al., 1977). These observations are consistent with the high content of mucin glycoproteins found in caecal digesta from germ-free but not conventional rats (Lindstedt et al., 1965; Hoskins and Zamcheck, 1968). Prizont and Konigsberg (1981) demonstrated fermentation of glycoproteins obtained from faeces of germ-free rats in supernatants from the caecum of coventional rats.

Variyam and Hoskins (1981) incubated hog gastric mucin in human faecal extracts and in anaerobic faecal cultures. They reported that after 48 h only 65 to 90% of mucin carbohydrates and 30 to 50% of mucin protein were degraded in faecal extracts while in anaerobic cultures 89 to 99% of the sugars and 20 to 81% of protein were degraded. After 96 h of incubation in two faecal cultures between 40 and 50% of mucin protein and 93 to 97% of mucin carbohydrates were fermented (Variyam and Hoskins, 1983). In another study (Miller and Hoskins, 1981) mucin hexose degradation exceeded 90% in more than half of the faecal cultures while mean protein degradation was only 65% after 48 h incubation.

A variety of glycosidases, produced exclusively by enteric bacteria, are required for the complete degradation of mucin oligosaccharide chains. These enzymes are primarily extracellular exoglycosidases that cleave terminal monosaccharides one at a time from the nonreducing end of oligosaccharide chains. A high degree of substrate specificity is determined by the monosaccharide to be removed, its anomeric configuration and the location of its glycosidic linkage to the next sugar (Hoskins, 1984). Evidence from Hoskins et al. (1983) and Bayliss and Houston (1984) indicate that a combination of bacterial species, each having a different set of enzymes, may be required for complete degradation of mucin glycoproteins. However, of the many different kinds of bacteria found in faeces only a small proportion, approximately 1%, are capable of degrading mucin glycoproteins (Miller and Hoskins, 1981; Bayliss and Houston, 1984; Stanley et al., 1986). These data support the premise that little, if any, digestion of mucin occurs prior to the large intestine.

CONTRIBUTION OF MUCIN TO ENDOGENOUS PROTEIN AND CARBOHYDRATE

Results from several studies indicate that mucin is the primary source of endogenous carbohydrates in ileal effluent. Mucin represents the majority of carbohydrate in canine Heidenhain pouches (Kowalewski et al., 1976). Englyst and Cummings (1986, 1987) reported that fucose and galactose represented about 65% of the total neutral carbohydrates in ileostomy effluent from humans consuming

nonstarch polysaccharide-free diets. Mucin carbohydrates, namely galactose, fucose and amino sugars, accounted for 77% of the total carbohydrates at the distal ileum of colectomized rats fed fibre-free diets (Monsma et al., 1992). More recently, it was reported that fucose, galactose, GalNAc, and GlcNAc represent more than 90% of total carbohydrate in the water-soluble, ethanol-precipitable fraction of ileal digesta from pigs fed a protein-free diet (Lien et al., 1997). In the aforementioned study, mucin represented approximately 74, 75, 53, and 100% of fucose, galactose, GlcNAc and GalNAc in ileal digesta, respectively. The low contribution of GlcNAc is probably due to the presence of proteoglycans. In ileostomates consuming increasing amounts of soya fibre more than 85% of endogenous fucose, galactose, GalNAc, and GlcNAc were derived from mucin (Lien et al., 1996). Interestingly, the outputs of endogenous carbohydrates, and thus mucin, were nearly twice as high in males compared to females.

The contribution of mucin to total endogenous protein was determined by estimating the mucin content in ileal digesta from pigs fed a protein-free diet and given either a complete amino acid mixture or saline intravenously (Lien et al., 1997). Protein in mucin represented only 5 to 11% of endogenous protein, depending on the infusion treatment and the degree of proteolytic degradation. However, the predominant amino acids in mucin, namely threonine, serine and proline, represented considerably higher proportions compared to the other amino acids, from 28 to 33%, 13 to 16% and 7 to 24%, respectively. It was suggested that these values might even be underestimated because of the high content of threonine in the soluble nonmucin protein fraction of digesta (Lien et al., 1997). This underestimation could result from the fact that these estimates were based on the assumption that mucin oligosaccharide chain elongation was relatively complete, whereas it is generally recognized that at elevated mucin secretions (as with consumption of food compared to fasting) there is incomplete elongation of oligosaccharide chains (Allen, 1981, 1984). These results are consistent with those obtained with protein-free diets, showing threonine to be the predominant indispensable amino acid in endogenous protein (e.g., Sauer et al., 1977). The presence of mucin in ileal digesta will, therefore, explain the low digestibilities of this amino acid in many feedstuffs fed to pigs (Sauer and Ozimek, 1986).

EFFECT OF DIET ON MUCIN SECRETION

Since mucin secretion is stimulated by many of the same neural and hormonal factors that control digestive processes (Allen, 1981; Neutra et al., 1982; Forstner and Forstner, 1986; Neutra and Forstner, 1987; Mantle and Allen, 1989), diet composition is expected to have considerable effects on mucin secretion. These effects might be indirect, *via* their influence on digestive processes, or direct, *via* their

interaction with the mucus gel. One of the more important indirect influences would be the secretion of proteolytic enzymes, since these are also stimulated by these same secretagogues (Heresy, 1987; Solomon, 1987). Mucin output (e.g., Kowalewski et al., 1976; Allen et al., 1980) and the proportion of mucin subunits (Allen et al., 1980) is increased in the presence of pepsin following the administration of stimulants. Mantle and Allen (1989) have suggested that the effects of some of these stimulants on mucin secretion may in fact be modulated by their effect on proteolytic enzyme secretion. The results from recent studies support previous reports that mucin secretion is regulated by many of the hormonal controls governing digestive processes. Insulin (Tabuchi et al., 1997), secretin (Tani et al., 1997), and gastrin (Ichikawa et al., 1993, 1998; Komuro et al., 1999) have been implicated as stimulants for mucus secretion.

The consumption of food increases mucus synthesis. The synthesis of gastric glycoproteins is reduced in fasted rats (Dekanski et al., 1975; Ohara et al., 1984). Kowalewski et al. (1976) reported a 50% increase in glycoprotein carbohydrate output in canine Heidenhain pouches following the consumption of a meal. This may have resulted from an increase in proteolytic degradation, since pepsin secretion was increased by 300%. Reducing food intake in rats to half their normal daily consumption resulted in a dramatic decrease in the amount of immunoreactive mucin (relative to protein and DNA) in intestinal scrapings (Sherman et al., 1985). Mariscal-Landin et al. (1995) reported that the total output of hexosamines (GalNAc plus GlcNAc) in ileal digesta were 6.8 and 6.9 mmol/kg dry matter intake in pigs fed a protein-free and a low protein diet, respectively. These values increased to 10.2 to 13.1 mmol/kg dry matter intake when the pigs received high protein diets.

Few studies have examined the effects of individual dietary constituents on mucin secretion. These studies focused primarily on the effect of dietary fibre; an interesting picture is emerging. Adaptation to diets high in fibre induce structural and morphological (Vahouny and Cassidy, 1986) and cytokinetic (Jacobs, 1986) changes in the digestive tract that indicate a capacity for higher mucin secretion, i.e. more mucin-secreting cells as a result of an increase in the surface area of the intestinal tract. Indeed, total daily ileal hexosamine outputs were approximately 1.5 g for 35 kg pigs (Mariscal-Landin et al., 1995) compared to 2.8 g for 55 kg pigs (Lien et al., 1997) fed protein-free diets of similar composition. Studies measuring synthesis or amounts of mucus in sections of the gastrointestinal tract suggest a greater secretion of mucus in animals fed diets containing insoluble rather than soluble fibre. Vahouny et al. (1985) reported an increase in incorporation of ^{35}S, 150 and 264%, and ^{3}H, 190 and 202%, into jejunal glycoproteins of rats fed diets containing 10% cellulose or 10% wheat bran, respectively, compared to rats fed a fibre-free diet. Much of this increase in radioactivity was associated with surface glycoprotein, particularly glycoprotein that was loosely associated (glycoproteins

recovered by washing the intestine compared that that recovered after rinsing or from tissue homogenates). Interestingly, the proportion of goblet cells was significantly reduced in rats fed the cellulose-containing diet, 9.7% compared to those fed either the fibre-free and wheat bran-containing diets, 13.2 and 13.6%, respectively. These results were later supported by Satchithanandan et al. (1989). In the aforementioned study, immunoreactive mucin in the lumen of the small intestine of rats fed a diet containing 10% wheat bran was 210% higher than in rats fed a fibre-free diet. The amounts of total immunoreactive mucin (lumenal plus tissue) were 230 and 200% higher in rats fed diets containing 10 and 20% wheat bran, respectively, compared to the fibre-free controls. The amount of lumenal immunoreactive mucin (acquired by aspiration of the mucosal surface) was higher, approximately 350 and 200%, in the stomach and small intestine, respectively, of rats fed a diet containing 5% citrus fibre, compared to those fed a fibre-free diet (Satchithanandan et al., 1990). However, there was no effect on the amount of lumenal immunoreactive mucin in any section of the gastrointestinal tract when the diet contained 5% guar gum. There was no effect either on the amount of immunoreactive mucin in gastric, small intestinal, and colonic tissues of rats fed a diet containing 5% citrus fibre. Satchithanandan et al. (1990) reported that the soluble fibre carrageenan also had no effect on the amount of small intestinal mucin.

More recent studies, however, suggest an opposite effect. Increasing amounts of pea fibre (0, 80, 160 and 240 g/day) were fed to pigs in addition to 1600 g/day of a wheat diet (Lien, 1995). Although there were no differences ($P > 0.05$) in ileal recoveries of mucin between diets, there was a linear trend ($P = 0.088$) towards an increase with increasing pea fibre consumption (Table 4). Exclusion of results from one pig, which were quite variable, resulted in a linear increase ($P < 0.05$) in mucin output with increasing fibre intake. The mucin recoveries were 6.1, 6.9, 7.3, and 7.8 g/day for diets supplemented with 0, 80, 160, and 240 g pea fibre/day, respectively. The ileal recoveries of total hexosamines increased linearly from approximately 3.5 to 7.5 mmol/kg dry matter intake per day in pigs fed protein-free diets containing 17, 34, and 102 g crude fibre/kg diet from wood cellulose, maize cobs, and wheat straw (Mariscal-Landin et al., 1995). Monsma et al. (1992) reported a 34% increase in mucin carbohydrate output in colectomized rats fed a diet containing 5% gum arabic compared to a fibre-free diet.

Observations that mucus secretion is elevated by insoluble but not soluble fibre are in contrast to those of Cassidy et al. (1981) who reported that feeding diets supplemented with either 15% pectin or lucerne to rats increased the percentage of intestinal villi exhibiting structural deviations by about 300% compared to rats fed chow. Neither 15% wheat bran nor cellulose appeared to have any effect on intestinal morphology. There was, however, a visual increase in adherent mucus and an apparent increase in goblet cell activity. The intestine responds to the consumption of soluble fibre such as guar gum and pectin by increasing crypt cell production

TABLE 4

Recoveries (g/d) of amino sugars in ileal digesta and faeces and total, gastric, and intestinal mucin in ileal digesta of pigs consuming either a protein-free diet or diets with increasing amounts of pea fibre supplemented to a wheat diet

	Protein-free[z]	Pea fiber intake, g/d[y]				
		0	80	160	240	SEM
Ileal amino sugars						
N-acetylgalactosamine	1.12 ± 0.30[x]	1.03	1.19	1.10	1.31	0.056
N-acetylglucosamine	1.72 ± 0.68	1.98	2.45	2.30	2.68	0.079
Ileal mucin[w]						
total	5.80 ± 1.49	6.18	7.25	6.76	7.78	0.469
gastric	1.45 ± 0.61	2.82	3.46	3.34	3.42	0.224
intestinal	4.35 ± 1.11	3.38	3.80	3.42	4.58	0.322
Faecal amino sugars						
N-acetylgalactosamine		0.30	0.43	0.49	0.63	0.016
N-acetylglucosamine		0.63	0.97	1.10	1.41	0.027

[z] Lien et al. (1997)

[y] Lien (1995)

[x] mean ± SD

[w] estimated from the GlcNAc/GalNAc ratio in crude mucin and the daily output of GalNAc in ileal digesta according to procedures outlined by Lien et al. (1997). All mucin in ileal digesta was assumed to be undegraded (native mucin)

rates (Jacobs, 1986; Johnson and Gee, 1986), presumably in response to the degree of damage as was reported by Cassidy et al. (1981). Similar increases in crypt cell production were not observed when oat bran was fed (Jacobs, 1983). Although Vahouny et al. (1985) did observe an increase in crypt cell proliferation and migration in the jejunum of rats fed a diet supplemented with wheat bran, Jacobs and White (1983) did not observe any effect of wheat bran. Crypt cell production rates increased in response to local cell damage (Rijke et al., 1976). These data, together with those presented for mucus secretion and output, give an indication of the effects of these different types of fibre in the gastrointestinal tract and mucosal response. It appears that insoluble fibre has a more abrasive action, scraping mucin from mucosa as they pass through the digestive tract. This abrasive action was demonstrated in a study by Lien et al. (1996) with ileostomates. Human ileostomates were given graded levels of soya fibre, from 1.1 to 33.7 g/day. While there was no relationship between daily outputs of GlcNAc and GalNAc and fibre intake, the outputs of these sugars increased linearly with increasing effluent dry matter output. In animals fed diets containing insoluble fibre the mucus layer may be maintained by increasing goblet cell activity and thus increasing the capacity

for mucin synthesis. This increase in goblet cell activity might account for the higher amounts of adherent mucus and increased incorporation of labels observed in previous studies with insoluble fibre (Vahouny et al., 1985; Satchithanandan et al., 1989, 1990). Soluble fibre, on the other hand, is far more damaging to the intestinal mucosa which must respond by re-establishing both the mucus and epithelial layers. The epithelial layer is repaired by increasing the rate of cell replacement. The mucus layer may be re-established primarily using mucin stored in crypt cells rather than by increased mucin synthesis. These changes may not be detected in isotope studies because mucin, that is stored, will not be labeled and because rats are fasted for 24 h prior to measurements, allowing the intestine sufficient time to repair itself (Silen and Ito, 1985). Since the amount of mucin in the mucus layer represents a balance between secretion and erosion, a measurement of both is necessary to obtain a more complete insight into the dynamic state of the mucus layer (Mantle and Allen, 1989).

In addition to these direct physical effects of fibre, secondary effects may also play a role in changes in mucin output. Although the activities of proteolytic enzymes in pancreatic juice do not appear to be influenced by diet (e.g., Low, 1982b; Żebrowska et al., 1983), studies by Schneeman et al. (1982) indicate that diets supplemented with different types of fibre affect the activities and distribution of proteolytic enzymes in the intestinal lumen that may influence the degradation of mucus gels. Trypsin and chymotrypsin activities were higher in intestinal contents and lower in mucosal homogenates of rats fed a diet containing wheat bran compared to a fibre-free diet (Schneeman et al., 1982). However, for pectin, enzyme activities were higher in mucosal homogenates and lower in intestinal contents (Forman and Schneeman, 1980). Guar gum increases total protease activity in the intestine (Poksay and Schneeman, 1983). Farness and Schneeman (1982) reported that oat bran, pectin, and cellulose increased small intestinal peptidase activities in rats by 12, 159 and 48%, respectively. The pepsin content in duodenal digesta of pigs fed a barley-soyabean meal diet was twice that of pigs fed a purified diet (maize starch and casein) diet (Żebrowska et al., 1983), which may result from the higher fibre content of the barley-soyabean meal diet. However, the extent to which these changes in proteolytic activities contribute to changes in mucin secretion and/or the recovery of mucin in ileal digesta after feeding fibre-containing diets is yet to be determined. Improvement in the protein status of pigs, either parentally (Lien et al., 1997) or enterally (Marisal-Landin et al., 1995), appears to increase mucin output, perhaps as a result of improvements in the proteolytic capacity of the digestive tract.

Lectins have become important and powerful tools in the study and characterization of gastrointestinal glycoproteins because of their selective carbohydrate-binding properties (Vecchi et al., 1987; Jauregui et al., 1991; Bals et al., 1997; Ohara et al., 1997). Conversely, Freier et al. (1985) were able to isolate lectins

from several different plants using immobilized hog gastric mucin. The ability of lectins, which are present in variable amounts in many feedstuffs, to bind glycoproteins has important consequences in the output of mucin in the gastrointestinal tract. In addition, Haas et al. (1999) observed that some lectins can induce histamine release, suggesting a secondary modulation of mucin secretion since histamine is a known mucus secretagogue. Moreover, lectins survive digestion in the gastrointestinal tract (Begbie and Pusztai, 1989) and may facilitate the movement of mucin into the large intestine. Some of the most commonly used feedstuffs for swine, including cereals (Marsh, 1992), soyabeans and legumes in particular (Begbie and Pusztai, 1989; Jauregui et al., 1991) contain lectins that have varying capacities to bind glycoprotein. In a recent study, pigs were fed a barley, a barley-bean (c.v. Great Northern beans), a barley-lentil and two barley-pea diets (Lien and Sauer, 2000). The sources of peas were line SS7 and c.v. Trapper which are high and low in trypsin inhibitor activities, respectively. Great Northern beans are characterized by a high lectin content. Consumption of diets containing SS7 peas and beans resulted in significant increases in the recovery of mucin in ileal digesta compared to diets containing barley alone or barley and Trapper peas or barley and lentils. In the same order for these diets, the ileal recoveries of mucin were 9.70, 14.01, 7.77, 7.15, and 7.42 g/day, respectively (Table 3). The high output of mucin with the bean-containing diet is not surprising since the toxic effects of lectins are well documented (Begbie and Pusztai, 1989; Kik et al., 1989; Vander Poel, 1990). However, the relatively high output of mucin following consumption of the diet containing SS7 peas was somewhat unexpected since these peas have a higher trypsin inhibitor content than Trapper peas. Further studies are required to elucidate factors in SS7 peas, including lectins, that contribute to the higher recovery of mucin in ileal digesta. The effect of these diets on the relative proportions of gastric and intestinal mucins in ileal digesta is also of interest. Mucin in ileal digesta of pigs fed the barley diet was derived primarily from the gastric mucosa (63.6%). The proportions of gastric and intestinal mucus in ileal digesta of pigs fed diets containing peas and lentils were similar (49.1 to 54.9% gastric mucin). The estimated high contribution of mucin derived from the gastric mucosa in pigs fed beans (89.4%) might, in part, reflect the recovery of GlcNAc from beans in ileal digesta. The diet with beans contained approximately 0.08% GlcNAc. Gastric mucin represented approximately 25% of mucin in ileal digesta of pigs fed a protein-free diet and approximately 50% of mucin in ileal digesta of pigs fed a wheat diet, without or with added pea fibre (Table 4).

Estimates of the recovery of mucin in faeces, compared to ileal digesta, are confounded by the secretion of mucin in the large intestine and bacterial fermentation of gastric and small intestinal mucins. Furthermore, amino sugars derived from bacteria will also confound these estimates. The relative recoveries of amino sugars in ileal digesta and faeces indicate that considerable fermentation of mucin

occurs in the large intestine (Tables 3 and 4). While the trends observed for the recovery of mucin in ileal digesta of pigs fed increasing levels of pea fibre were also evident to those for amino sugar recoveries in faeces, this was not the case for amino sugar recoveries in faeces of pigs fed legumes. Although the higher output of mucin of pigs fed the bean-containing diets is indicated by higher faecal amino sugar outputs, the difference compared to the other diets is not as great as in ileal digesta. Whereas increasing recoveries of amino sugars in ileal digesta, following the consumption of increasing amounts of pea fibre, indicate an increase in gastric and small intestinal mucin secretion, the recoveries of amino sugars in faeces might be explained by activities specific to the large intestine. Shiau and Chang (1983) reported that the specific activity and total output of mucinase in faeces of rats was negatively correlated with the availability of fermentable carbohydrate in different sources of fibre. The highest outputs of specific and total mucinase activities were observed in faeces of rats fed fibre-free and cellulose diets and lowest in rats fed the more readily fermentable fibres, carrageenan, pectin and guar gum. For more fermentable fibre, such as pectin and guar gum, the faecal output of mucinase was lower, although not significantly, with consumption of diets containing 15 vs 5% fibre. In a second study, a decrease in total and specific faecal mucinase activities was observed as the proportions of cellulose and agar (resistant to fermentation) were increased in the diet (Shiau and Ong, 1992). The highest mucinase activities were observed in faeces of rats consuming either a fibre-free or 15% agar diet, followed by those consuming a 7.5% agar/7.5% cellulose diet and finally by those consuming a 15% cellulose diet. As more readily fermentable carbohydrate enters the large intestine there is a reduction in fermentation of gastrointestinal mucins, and thus a potential increase in the recovery of mucin in faeces. In addition, short-chain fatty acids produced during fermentation of fibre in the large intestine stimulate the release of mucin from the colon (Sakata and Setoyama, 1995), augmenting the effects of fibre fermentability on faecal mucin output. It is apparent, therefore, that faecal estimates of mucin outputs are greatly influenced by the action of microbes in the large intestine. In contrast, mucin outputs at the distal ileum better reflect the net effect of diets in the stomach and small intestine in terms of both physical interactions and effects on digestive processes. These results indicate that the effect of diet on mucin secretion is better reflected by estimates obtained in ileal digesta rather than in faeces.

CONCLUSIONS

Mucus is a large molecular weight glycoprotein that provides a protective lining for the entire gastrointestinal tract. Once secreted into the intestinal lumen little degradation of mucus occurs prior to the large intestine. In this respect lume-

nal mucin adds an extra level of protection by acting as a lubricant. The recovery of undegraded mucin in ileal digesta can provide important insights into the effects of diets and dietary constituents on the gastrointestinal tract. In addition, measurement of the recovery of mucin in ileal digesta provides information for the assessment of the recovery of endogenous protein to determine true digestibility. As such, there is growing interest in elucidating dietary factors that influence gastric and intestinal mucus secretion and recovery in ileal digesta. While it is apparent that dietary constituents such as fibre and lectins can have a direct effect on mucus secretion, it is also important to consider indirect effects and their consequences to the mucus layer.

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STRESZCZENIE

Wpływ diety na sekrecję i degradację mucyn w przewodzie pokarmowym zwierząt monogastrycznych i człowieka

W opracowaniu przedstawiono stan dotychczasowych badań nad wpływem diety na sekrecję mucyn i ich zawartość w treści jelita biodrowego. Opisano ogólną strukturę mucyn i ich degradację w jelicie cienkim i grubym. Mucyny, będące ochronną warstwą całego przewodu pokarmowego, podlegają działaniu wszystkich chemicznych i fizycznych czynników trawiennych. Najważniejszym z nich jest proteolityczny rozkład mucyn do mniejszych cząstek, a następnie ich uwalnianie do światła jelita. Ubytki mucyn uzupełniane są przez ich syntezę i sekrecję z dolnych warstw nabłonka. Diety mogą wpływać na ten proces pośrednio przez ich oddziaływanie na procesy trawienne, z których najważniejszym jest ilość i rozmieszczenie enzymów proteolitycznych w świetle jelita, a także bezpośrednio poprzez siły fizyczne wywierające nacisk na nabłonek przewodu pokarmowego. Stwierdzono zmiany zdolności przystosowania aktywności w komórkach kubkowych w zależności od rodzaju skarmianej diety. W świetle jelita cienkiego stwierdzono tylko niewielką degradację mucyn, natomiast w jelicie grubym mucyna jest fermentowana przez zasiedlającą to jelito populację drobnoustrojów. Zawartość nie rozłożonej mucyny w treści jelita biodrowego ma duże znaczenie w badaniach żywieniowych: po pierwsze ze względu na to, że może powodować znaczne straty aminokwasów endogennych i węglowodanów, po wtóre, że może zmieniać oddziaływanie diet na przewód pokarmowy.