The guts of the matter: dietary regulation of intestinal gene expression

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Summary

The ability of animals to adapt to fluctuations in dietary nutrients is critical for their survival. Adaptation is mediated to a large extent by the gastrointestinal tract, which has an inherent ability to cope with variation in the type and concentration of dietary nutrients. This adaptation occurs by modifications in the permeability and structure of the brush border membranes and by altering the state of the carrier transporters.

Although dietary nutrients have been shown to exert pronounced effects on gene expression in most tissues and organs (Berdanier and Hargrove 1993), there is little experimental evidence demonstrating that these nutrients also have a direct effect on gene expression within the gastrointestinal tract. The aim of this review is to discuss the limited evidence that is currently available on the effects of dietary protein, fat, carbohydrates, vitamins and minerals on intestinal gene expression. With new molecular tools becoming increasingly utilised, more extensive studies on the gene expression in the gut should be forthcoming.

Keywords: gene expression, gut, nutrient, intestinal genes, diet, protein, fat, carbohydrate, vitamin, mineral

Introduction

Genes, the environment and their interactions determine the phenotypes of organisms. Evolutionary theory postulates that genetic mechanisms are inherited from ancestral patterns that have been modified by mutation and natural selection during competition for limited resources. Nutrients can be defined as any compound necessary for or contributing to the metabolism of an organism. Hence, these compounds are crucial if resources are limited, and the ability of an organism to react to changes in nutrient availability is crucial for survival. However, there is a paucity of information on the effect of nutrients on gene expression in the gastrointestinal tract and the long–term consequences that result from elevated or inadequate nutrient intake on animal health, well–being and production.

The intestine is the major site of nutrient uptake and the gastrointestinal tract adapts both morphologically and functionally to internal and external environmental fluctuations in the nutrient supply. This adaptation includes modifications in the fluidity and permeability of brush border membranes and changes in carrier–mediated transport. Recent evidence suggests that the dietary nutrient supply can also effect gene expression in the intestine (Levi and Sanderson, 2004).

Over 40 nutrients are known to be essential to mammals, and a deficit and/or an excess of many nutrients will impair livestock health and production. It is believed that nutrient regulation of intestinal genes enables an organism to adapt to variations in nutrient supply and avoid the potentially deleterious consequences thereof. In some cases, this regulation of gene expression may be instigated by receptors that detect the presence of nutrients or the presence of hormones secreted in response to the nutrients. In other cases, dietary regulation of gene expression may involve a transducing mechanism in which cellular activity is affected by the presence of specific nutrients and this change in cellular activity alters gene expression (Sanderson and Naik 2000). Whatever the mechanism, it is clear that gene expression can be influenced by the concentration of particular nutrients in the diet. The aim of this review is to collate current knowledge on the effects of specific nutrients on the expression of genes in the digestive tract. Notably, to date, most of the studies have examined the expression of individual genes using quantitative PCR rather than examining global gene expression using microarray analysis or differential display.

Dietary nutrients

All living organisms require essential nutrients for tissue maintenance and repair, growth, reproduction, lactation and work. Compounds in animal feeds have complex chemical structures that must be broken down to smaller components by physical and chemical processes before

they can be absorbed. Most livestock species can be classified as ruminant or monogastric on the basis of the anatomy of the digestive tract. Although the digestive tracts of these species evolved to utilise vastly different types of substrates, tissue requirements for nutrients are similar across species. Nutrients are commonly classified as protein, lipid, carbohydrate, and vitamin or mineral, all of which may affect intestinal gene expression (Sanderson and Naik 2000).

Proteins, amino acids and gene expression

An adequate supply of high quality dietary protein is important for growth and resistance to infectious diseases. The amino acids that are absorbed after digestion of dietary proteins serve as building blocks for protein synthesis in the tissues of the animal and as a source of nitrogen. Restriction of dietary protein reduces the growth rates of young animals and low protein diets have been shown to alter mRNA levels in various organs and tissues. Hesketh *et al.* (1998) reported that a number of genes respond to dietary protein concentration changes with the effect taking place at the post–transcriptional phase. However, dietary protein content also has been shown to affect gene transcription. For example, Delghingaro–Augusto *et al.* (2004) studied the effects of a low protein diet on gene expression in rat pancreatic islets using macroarray analysis and RT–PCR, and showed that low protein diets induced changes in the expression of 32 genes related to metabolism, neurotransmitter receptors, protein trafficking and targeting, intracellular kinase networks and hormones.

The effect of a low dietary protein supply on growth rate appears to be mediated through growth factors such as insulin–like growth factor (IGF) and the insulin–like growth factor binding proteins (IGFBP) (Noguchi, 2000). Therefore, dietary protein may influence intestinal gene expression indirectly by affecting distal expression of hormones and their receptors in such tissues as the pancreas.

Endo *et al.* (2002) showed using microarray analysis that protein quality also has an impact on global gene expression. In this study, rats were fed a protein–free diet or a diet containing either casein or gluten as the main source of protein. The authors observed that the protein–free diet altered the expression of 281 genes compared to the casein diet. On the other hand, wheat gluten diet altered gene expression in 111 genes compared with the casein diet. The differentially expressed genes were associated with growth, metabolism, signal transduction and cell structure. Genes associated with cholesterol metabolism were particularly responsive to changes in dietary protein content. Interestingly, the expression profiles of many genes were similar for the protein–free and gluten diets.

The effects of dietary protein on gene expression may be mediated by the structure or the composition of proteins. Endo *et al.* (2002) postulated that the effect of dietary gluten on the expression of genes associated with cholesterol metabolism was due a relative deficit of lysine and threonine. However, the data must be interpreted carefully. In the study of Katsumata *et al.* (2002), a low lysine diet (7 g/kg body weight) decreased growth rates, feed efficiencies and plasma IGF–1concentrations in pigs. Nevertheless, hepatic IGF–1 mRNA levels did not differ between the treatment groups, suggesting that the effect of lysine may be due to post–transcriptional events.

In addition to these few studies on global gene expression, there are several reports on the intestinal expression profiles of specific genes or gene families. As an example, Cheng *et al.* (2005) examined the expression profile of the PepT gene family in the intestine of chickens using Northern blot analysis. PepT is the term given to a family of membrane proteins that are responsible for the selective translocation of small peptides across cell membranes. The expression of PepT genes was measured in the duodenum, jejunum and ileum from day 16 of the embryonic development until the day of hatch. The authors demonstrated that a low protein diet (12% crude protein) specifically decreased the PepT1 mRNA abundance, and they concluded that the expression of PepT1 mRNA is regulated by dietary protein intake and stage of development.

The few studies thus far conducted demonstrate that both the type and concentration of dietary protein can affect gene expression in the gut. However, the regulation of intestinal gene expression by dietary amino acids and protein is poorly documented and clearly requires further research.

Lipids and gene expression

Lipids are a source of energy and an essential structural component of cells. Lipids also regulate the expression of genes associated with cell growth and differentiation, as well as many genes associated with protein, lipid and carbohydrate metabolism (Jump 2004). Most research on the effects of dietary lipids on gene expression relates to the distal tissue metabolism. Although dietary fat has been shown to affect intestinal gene expression in a few cases, there is little data on these effects.

Most of the research on the effects of dietary fat on intestinal gene expression has investigated individual genes. For example, Chelikani *et al.* (2004), using RT–PCR, found that the duodenal expression of the cholecystokinin (CCK) gene in Holstein cows was increased by canola oil. This corresponded with an increase in the plasma concentration of CCK.

In another example, Fisher *et al.* (1988) studied the effects of dietary saturated fatty acid on the gene expression of apolipoprotein B (apo B) in the intestine and liver of rabbits. Apo B is present in two isoforms, apo B–48 and apo B–100. Apo B–100 is a ligand for the LDL receptor. Apo B–48 is present in chylomicrons,

which play an essential role in the absorption of dietary fatty acids from the intestine (Green and Glickman 1981). Fisher *et al*. (1988) observed a twofold increase in intestinal apo B mRNA concentration two hours after the consumption of saturated fatty acids, indicating that fatty acids can directly affect the transcription of this gene.

Dietary long chain fatty acids also increased the level of cellular retinol–binding protein II (CRBP II) mRNA in the jejunum of rats (Goda *et al*, 1994). CRBP II is an abundant intestinal cytosolic protein, which binds to hydrophobic retinoids and facilitates their absorption and incorporation into chylomicrons. The regulation of CRBP II gene expression by long chain fatty acids is thus important for effective vitamin A absorption (Lissoos *et al*. 1995).

In addition, long chain fatty acids influence the expression of genes that code for fatty acid binding proteins in the intestine and liver as shown by Northern blot analysis (Poirier *et al*. 1997). Mice fed sunflower oil, which contains high concentrations of linoleic acid, exhibited elevated fatty acid binding protein mRNA concentrations in the duodenum and proximal jejunum. Long– to medium–chain triacylglycerols elevated levels of sucrose–isomaltase mRNA in the rat jejunum (Yasutake *et al*. 1995).

These reports demonstrate that dietary lipids can regulate the cytosolic levels of the proteins associated with nutrient transport in the intestine via changes in gene expression. However, while these gene expression studies have investigated the effects of the types of dietary lipid (e.g., saturated versus unsaturated fatty acids, long versus short chain fatty acids), the effects of altering the concentration of total lipids in the diet has not been explored. Moreover, the studies have focused on individual genes rather than the effects on global gene expression.

Carbohydrates and gene expression

Dietary carbohydrates are a major source of energy and include starch, cellulose, and gums that contain carbon, hydrogen and oxygen in similar proportions. Specific transporters and enzymes drive the absorption and metabolism of carbohydrates in the gut. Changes in the gene expression of these transporters and enzymes in the gut appear to occur in direct response to the composition and concentration of carbohydrates.

For example, dietary carbohydrates influence active monosaccharide transport in mice by altering the intestinal gene expression of the saccharide transporters (Diamond *et al*. 1984). A carbohydrate–free diet was shown to result in an increased rate of D–glucose uptake in the duodenum, jejunum and ileum, while a high–carbohydrate diet only stimulated uptake from the duodenum and jejunum. The authors demonstrated that dietary carbohydrates induced the specific expression of disaccharidases and monosaccharide transporters along the intestine. Chronic consumption of high–carbohydrate diets also increases the number of intestinal glucose transporters in rats, mice, sheep and humans (Ferraris, 2001).

Sucrase–isomaltase (EC 3.2.1.48) is an enterocyte–specific small intestine brush–border membrane disaccharidase that is required for hydrolysis of dietary sucrose and some starches. Lactase–phlorizin hydrolase (EC 3.2.1.23/62) is also specific to the intestine and hydrolyses lactose, phlorizin and glycosylceramides (Montgomery *et al*. 1991). Northern blot analysis of indicated that mRNA expression of both these enzymes is elevated by dietary sucrose in rats (Goda *et al*. 1995; Yasutake *et al*. 1995). Goda *et al*. (1999) observed that dietary sucrose altered the intestinal distribution of these enzymes, with a corresponding increase in mRNA levels of sucrase–isomaltase in the lower villus and lactase–phlorizin hydrolase in the mid– and upper villus.

Although in most studies only individual genes have been examined, a general pattern of carbohydrate effects on intestine gene expression has emerged. The effects of dietary carbohydrates appear to be mainly associated with regulation of carbohydrate transporters and the enzymes responsible for the digestion of complex carbohydrates to monosaccharides.

Vitamins and gene expression

Vitamins are required for metabolism, growth, development, and regulation of cell function. Vitamins exert many effects on gene expression in body tissues. As examples, vitamin A regulates the expression of genes associated with adipogenesis and brown adipose tissue thermogenesis (Bonet *et al*. 2003). Vitamin D can up–regulate or down–regulate the expression of genes involved in cell proliferation, differentiation and mineral homeostasis (Lowe *et al*. 1992). Vitamin E modulates pathways of cell signalling and gene expression (Hacquebard and Carpentier 2005).

Vitamins also exert effects on gene expression in the intestine. For instance, the effects of vitamin A on the gut have been studied extensively. Vitamin A and its precursors regulate the activity of β, β–carotene 15,15'–monooxygenase (βCMOOX), which catalyses the conversion of carotenoids such as β–carotene to retinal. Bachmann *et al*. (2002) found a dose–dependent decrease in intestinal activity of βCMOOX in response to oral administration to rats of retinyl palmitate, β–carotene, apo–8'–carotenal, all–*trans*–retinoic acid or 9–*cis* retinoic acid. This effect was not observed in the liver, suggesting that intestinal regulation of βCMOOX activity is independent of hepatic vitamin A status.

Gene expression in the colon is also affected by vitamin A. Nur *et al*. (2002) used microarray analysis to compare colon gene expression responses to diets with deficient versus adequate levels of vitamin A in healthy rats and in rats in which colitis had been induced. Gene expression of vitamin A deficient rats was similar to that of rats in which colitis had been induced. The results

suggest that vitamin A deficiency affects genes that are involved in inflammation of the colon.

Diets that are deficient in vitamin A also decrease mRNA expression of the apolipoprotein AI and CIII genes, which play a role in lipid transport in blood (Nagasaki *et al*. 1994). This effect was observed in the rat intestine but not in the liver. The authors concluded that gene expression of apolipoproteins is regulated by vitamin A in a tissue–specific manner and speculated that vitamin A may modulate lipid transport by altering apolipoprotein levels.

In vitro studies have shown that β–carotene down–regulates the expression of cyclooxygenase (COX–2), an enzyme that plays a putative role as a causative factor in colon carcinogenesis (Palozza *et al*. 2005). β–Carotene decreased COX–2 expression in colon cancer cells, which was accompanied by increased apoptosis. This suggests that the anti–tumour properties of β–carotene may be related to its ability to suppress expression of COX–2.

There is much less evidence that other vitamins can affect intestinal gene expression. Brehier and Thomasset (1990) studied the regulation of calbindin–D9K (CaBP9K) gene expression by vitamin D in the foetal rat duodenum. CaBP9K is associated with calcium transport. The authors showed that vitamin D and calcium can stimulate CaBP9K gene expression. Hall and Norman (1990) investigated the expression of the calbindin–D28 gene in the intestines of vitamin D deficient chickens. They found that levels of calbindin D28K mRNA were not affected by the diet unless vitamin D3 was administered. Vitamin D administration elicited a 28–fold increase in calbindin D28K mRNA concentrations in the tissues of the duodenum. These authors concluded that calcium is unable to modulate expression of the calbindin D28K gene in the absence of vitamin D3.

Vitamins appear to regulate gene expression in a tissue–specific manner. In addition, vitamins often act in conjunction with other nutrients to amplify their effects. Vitamin precursors such as carotenoids and retinoids also regulate intestinal gene expression. However, with the exception of vitamin A, very few studies have been conducted on the effects of vitamins on intestinal gene expression. A better understanding of these mechanisms may be of significance for animal feeding systems in which reliance is placed on a single source to fulfil the requirements for a particular vitamin.

Minerals and gene expression

Minerals function as catalysts in nerve responses and muscle contraction, as regulators of electrolyte balance and hormone synthesis, and as components of skeletal structures. Minerals can also affect gene expression. Zinc, copper, iron, selenium and phosphorus are among the many minerals known to alter gene expression. For instance, zinc deficiency specifically up–regulates expression of uroguanylin in the gut (Blanchard and Cousins 2000). Uroguanylin, a member of the natriuretic peptide hormone family, is secreted into the lumen of the gastrointestinal tract and regulates fluid balance (Forte and Currie 1995). The fact that uroguanylin mRNA concentrations are increased in zinc deficient animals suggests that zinc deficiency may cause or potentiate diarrhoea. Blanchard *et al*. (2001) used cDNA microarray analysis to monitor the expression profiles of genes affected by zinc deficiency in the small intestine. The mRNA levels of zinc–regulated genes such as metallothionein 1, zinc transporter 2 and uroguanylin were altered in accord with previous reports, but this study showed that other intestinal genes are also affected. These include genes associated with signalling pathways, growth, transcription, redox reactions and energy metabolism (Blanchard *et al*. 2001).

Dietary phosphorus affects intestinal gene expression of fish (Sugiura and Ferraris 2004). Rainbow trout were fed a low phosphorus diet or phosphorus adequate diet for 2, 5 or 20 days. The ratio of mRNA levels was used to evaluate the influence of diet on gene expression. The authors identified 30 genes that had responded to dietary phosphorus status by day 20; these included genes for intestinal meprin, cysteinesulfinic acid decarboxylase, renal S100 calcium binding protein, mitochondrial Pi carrier, caecal apolipoprotein E, somatomedin B–related protein and NaPi–II. Some of these genes were not previously associated with phosphorus deficiency. The authors concluded that the expression profile of early–response genes could be different to the profile of late–response genes.

It has been hypothesised that copper and iron modulate the same genes in the intestine. Marzullo *et al*. (2004) used differential display RT–PCR to identify genes that are regulated by these minerals. Rats were fed a control diet, a copper deficient diet or an iron deficient diet. Differential expression between treatments was observed for five cDNA fragments. Both metals regulated cytochrome c oxidase subunit II, copper down–regulated the Ebnerin–like gene and iron affected expression of glucocorticoid–regulated kinase. These findings are the first demonstration of a functional link between these two minerals at the level of regulation gene expression.

Collins *et al*. (2005) used microarray analysis and real–time PCR to demonstrate that genes responsible for intestinal iron absorption in rats were affected by an iron–deficient diet. The genes affected included those encoding the iron transport proteins, transferrin receptor 1 and heme oxygenase 1. Genes not previously identified with iron transport were also induced by iron deficiency (e.g., Menkes copper ATPase and metallothionein). The authors speculated that iron deficiency results in increased intestinal copper absorption.

Protein kinase C (PKC) belongs to the serine/threonine protein kinase family, and plays a role in transmembrane signalling events and in cellular proliferation and differentiation. Low dietary copper intake decreases PCK α protein expression in the

intestine but does not affect PCK δ and PCK γ (Davis and Johnson 2002). In addition, copper affects gene expression of PCK in the intestines of healthy rats but not in those with colon tumours.

Rao *et al*. (2001) examined intestinal gene expression responses to a low selenium diet in mice with oligonucleotide microarrays. The low selenium diet activated the genes associated with DNA damage, oxidative stress, cell cycle control and deactivated the genes involved in detoxification. Thus, a low selenium diet drastically alters cellular activity and tissue metabolism.

These results confirm that insufficient intake of a single trace element can have a broad impact on gene expression patterns. This is clearly demonstrated by studies in which microarrays or differential display methods have been used. The power of these methods is that a more global picture of the effects of these elements on gene expression can be drawn.

Implications of the effects of dietary nutrients on gene expression for animal health and production

A better understanding of the effects of dietary nutrients on intestinal gene expression would facilitate the formulation of diets for optimum animal health and production. The application of new methodologies that have been developed for proteomics and functional genomics (e.g., microarrays, differential display) presents an opportunity for the systematic investigation of the control of dietary nutrients on intestinal gene expression. As the research on trace minerals has demonstrated, previously unidentified pathways and mechanisms can be uncovered using these approaches.

It is clear that dietary nutrients influence intestinal genes that affect health. For example, dietary lipids can induce coronary artery disease, atherosclerosis, dyslipidemia, inflammation, obesity, diabetes, cancer, depressive disorders and schizophrenia via regulation of nuclear transcription factors or genes such as lipooxygenase, cyclooxygenase, protein kinase C or sphingomyelinase (Jump 2004). In addition, minerals such as zinc, which is associated with diarrhoea (Blanchard and Cousins 2000), and selenium, which is associated with oxidative damage (Rao *et al*. 2001), are powerful gene activators. Vitamins such as vitamin A can affect inflammation of the colon via changes in gene expression (Nur *et al*. 2002).

Nutrients also affect the quality of animal products. For example, the regulation βCMOOX by vitamin A may have consequences for meat quality. Decreased expression of this enzyme in cattle may attenuate the conversion of dietary carotenoids to vitamin A and increase their deposition in adipose tissue, causing an undesirable yellow colouration of fat (Kruk *et al*. 1998). Low intakes of vitamin A may increase

marbling (intramuscular fat deposition) in cattle, which is considered desirable by some Asian consumers (Oka *et al*. 1998).

The effects of dietary nutrients on the expression of genes associated with animal health and production has thus far focused on distal organs and tissues, and little attention has been paid to the gastrointestinal tract. The emerging field of gut nutrigenomics has only began to be explored, as new molecular tools have become available. The results to date suggest that majority of dietary nutrients are 'the guts of the matter' in terms of the regulation of intestinal gene expression.

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