Published in final edited form as:

Physiol Behav. 2014 September ; 0: 74–78. doi:10.1016/j.physbeh.2014.03.026.

Nutrient-induced intestinal adaption and its effect in obesity

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Abstract

Obese and lean individuals respond differently to nutrients with changes in digestion, absorption and hormone release. This may be a result of differences in intestinal epithelial morphology and function driven by the hyperphagia or the type of diet associated with obesity. It is well known that the maintenance and growth of the intestine is driven by the amount of luminal nutrients, with high nutrient content resulting in increases in cell number, villi length and crypt depth. In addition, the type of nutrient appears to contribute to alterations in the morphology and function of the epithelial cells. This intestinal adaptation may be what is driving the differences in nutrient processing in lean versus obese individuals. This review describes how nutrients may be able to induce changes in intestinal epithelial cell proliferation, differentiation and function and the link between intestinal adaptation and obesity.

Keywords

intestine; adaptation; stem cells; diet; obesity

1. Introduction

A myriad of differences in the morphology and function of the intestine have been documented between lean and obese individuals. The length of the intestine is longer in obese humans and other animals ^{1,2}. Obese humans have increased enterocyte (absorptive cell) mass ³ and increased intestinal permeability ⁴. Animal models of obesity have been able to reveal similar findings and have shown additional cellular differences. After a brain lesion to the ventromedial nucleus of the hypothalamus (VMH) in laboratory rats, a method that produces obesity, intestinal cell hyperplasia and greater villi length occurs compared with the sham-lesion, lean animals ⁵. Obese mouse models also show an increase in intestinal absorption ⁶ and permeability ⁷. It appears that the intestinal adaptation in these animals may be due to the hyperphagia that occurs in all models (VMH lesions ^{6,8},

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Disclosure

There are no conflicts of interest to declare.

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ob/ob^{6,9} and db/db¹⁰ mice, goldthioglucose⁶). Since Mayer and Yannoni⁶ had postulated that it is the hyperphagia that occurs with obesity, regardless of the etiology, that results in adaptive changes in the intestine, it has become well established that luminal nutrients are necessary for the growth of the mucosal epithelium. Increasing the luminal nutrient content using a variety of experimental methods increases the cell proliferation rate, cell number, villi length and crypt depth [methods include: intestinal resection/transposition¹¹, hyperphagic animals models, such as lactation¹² or cold exposure^{13,14}]. Whereas, the exclusion of luminal nutrients does the opposite [methods include: fasts¹¹, surgical bypass^{15,16}, hibernating animals¹⁷, total parenteral nutrition^{18,19}]. Moreover, this effect of luminal nutrients appears to be independent of body weight and systemic factors. Even in obese humans, caloric restriction alone is able to decrease the proliferation rate of colonic epithelial cells and this effect is unrelated to the body mass index or body composition²⁰. Thus, the amount of luminal nutrients may drive the differences in intestinal morphology and function seen between lean and obese individuals. One can imagine a multitude of ways by which changes in the intestinal epithelium may alter digestion, absorption and downstream processing of nutrients. This review will focus on 1) how nutrients may be able to drive increases in epithelial cell proliferation and differentiation, 2) the importance of the type of nutrient in intestinal epithelial function and 3) how this relates to differences in nutritional processing in obese versus lean individuals.

2. Intestinal epithelial cell proliferation and differentiation

The intestinal epithelium undergoes a process of continual renewal with a 3–5 day turnover rate in humans²¹. This process is characterized by active proliferation of stem cells localized near the base of the crypts, progression of these cells up the crypt–villus axis, cessation of proliferation and subsequent differentiation into one of the many cell types (*ie.* enterocytes, goblet cells, Paneth cells, enteroendocrine cells, M cells, Cup cells, tuft cells; Fig. 1). In the process of differentiation, these cell types acquire structural features of mature cells and all but the Paneth cells continue to move up the villus towards the tip. As the mature cells reach the villus tip, they undergo apoptosis and are extruded into the lumen as new differentiated cells take their place. The cellular mechanisms controlling epithelial proliferation and differentiation have not been clearly defined, but leave multiple routes by which nutrients may modulate this process.

2.1 Diet-induced modulation of stem cells

Although the exact number and location of stem cells is still unclear²², at least two pools of stem cells have been identified in mammals that differ in their position, expression of specific markers and cell cycle characteristics. The crypt base columnar cells (CBCs) are located in every crypt base and express the leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) stem cell marker²³. The other identified stem cell population is located outside of the crypt base in the +4 position, is sparsely located in the intestine and expresses the Polycomb group protein Bmi1 stem cell marker²³. These two stem cell populations appear to be functionally distinct and utilize different intracellular signals to undergo proliferation. The Lgr5 stem cells are mitotically active, destroyed by radiation (which decreases the chance for genetic mutations being passed to daughter cells) and utilize the

canonical Wnt/ β -catenin signaling pathway to increase proliferation²³. In contrast, the Bmi1 population is normally quiescent, becomes active after irradiation or injury and may not utilize Wnt signaling²³. The Wnt/ β -catenin signaling appears to be important in maintaining normal regenerative capacity of the intestinal epithelium because disruption of signaling results in atrophy or disorganization of the crypts and villi²⁴. Conversely, activation of this pathway results in an increase in cell proliferation and is common in colon cancers²⁵. It is unclear whether luminal nutrients can gain direct access to these stem cells and modulate cell proliferation signaling, but data support the role (whether direct or indirect) for stem cells and Wnt signaling in diet-induced intestinal adaptation.

Investigations into the effect of the Wnt/ β -catenin signaling pathway in intestinal adaptation have been carried out using two hyperphagic mouse models, *db/db* obese mice and high-fat diet induced obese mice²⁶. In both cases, β -catenin protein expression is increased in the jejunum of the intestine²⁶. This effect corresponds with an increase in the proliferation of intestinal epithelial stem cells, villi length and nutrient absorption. These effects are reversed by food restriction in *db/db* mice and by the administration of a β -catenin inhibitor in high-fat diet induced obese mice that showed no significant difference in body weight²⁶. These data do not include an investigation into whether Wnt signaling is specifically altered in Lgr5 stem cells or an analysis of Wnt signaling along the proximal to distal axis of the intestine. In a separate investigation in the large intestine of mice, a location specific effect of high fat diet on Lgr5 gene expression was found. Lgr5 is down-regulated in the proximal colon over time at 8 and 16 wks on the high-fat diet, but not on the low-fat diet²⁷. In contrast to the proximal colon, Lgr5 expression in the distal colon is elevated over time of high-fat feeding²⁷. We know that the digestive function of cells along the intestinal axis differ and this must somehow be reflected in the regenerative process of the epithelium. This may include a localized effect of nutrients on stem cell proliferative processes or a varying effect of nutrients on the Lgr5 or Bmi1 stem cells along the intestinal axis.

2.2 Direct nutrient effect on stem cell proliferation

It is not known where in the Wnt signaling pathway nutrients play a role, but may include greater induction of Wnt proteins from neighboring cells, facilitating Wnt binding to its receptor on the Lgr5-positive stem cells or through modulating the Wnt signals intracellularly. Glucose can control β -catenin through a cAMP/PKA pathway²⁸ or by increasing β -catenin acylation and translocation to the nucleus²⁹ in other stem cell populations (Fig. 2). Fatty acids (*ie.* palmitoleic acid), on the other hand, may increase Wnt secretion from neighboring cells³⁰ (Fig. 2). These nutrient-induced changes in Wnt signaling would result in greater cell proliferation and could account for the diet-induced changes in intestinal morphology and function described above. The story is far from clear, though. Multiple studies show that fatty acids, including palmitate³¹ and omega-3 polyunsaturated fatty acid³², decrease Wnt/ β -catenin signaling in various stem cell populations. In particular, stearic and palmitic acid inhibit Wnt signaling by binding to the Wnt inhibitor factor 1³³. This action of fatty acids goes against the data showing a diet-driven hyperplasia of the intestine and suggests a specific fatty acid effect or the role of other mechanisms.

2.3 The effect of diet on epithelial division and differentiation

The stem cell-derived progenitor cells continue to divide and then differentiate as they move from the crypt to the villus (Fig. 1). While still in the crypt, the progenitor cells are termed transit amplifying cells because they undergo multiple mitotic divisions before they begin to differentiate. Although the TA cells continue to utilize the Wnt/ β -catenin pathway in the division and differentiation processes³⁴, studies emphasize the role of Notch signaling in directing epithelial lineage allocation^{35,36}. Math1 and Hes1 are two downstream transcription factors that work in opposition to each other to drive the differentiation into secretory cells (*ie.* enteroendocrine, goblet) or enterocytes (Fig. 3). Math1 is required for the differentiation of the secretory lineages³⁵. In Math1 knockout mice, the architecture of the crypt-villus is normal but the villi are comprised only of enterocytes³⁵. Further specification is directed by neurogenin3 (ngn3), which is downstream of Math1 and directs enteroendocrine differentiation from goblet cells³⁷. In contrast to Math1 and ngn3, Hes1 supports the differentiation into enterocytes³⁶. It is possible that nutrients may influence TA cell division or commitment to particular cell lineages because high-fat fed mice have a decrease in the number of goblet cells, despite an increase in overall epithelial number compared with mice on a control diet³⁸. Nutrients may influence the differentiation process in a way that results in an unbalanced ratio of the various epithelial cell types. Whether there is a differential increase in certain cell types or an equal increase across cell types, the nutrients may drive these effects through various intracellular mechanisms that include these Notch transcription factors involved in progenitor proliferation and differentiation.

3. Function of the mature epithelial cells

3.1 Enterocytes

The increase in enterocytes that occurs in obesity, or other conditions of increased luminal content, equates to an increase in the absorption of nutrients. The capacity for greater absorption, though, is specific to the nutrient component of the maintenance diet^{39,40}. Obese mice that normally consume a high carbohydrate diet exhibit greater absorption of glucose compared with their lean counterparts⁶. When these mice are switched to a high fat diet, they no longer exhibit an increase in glucose absorption⁶. The reverse also is true in obese mice maintained on a high fat diet⁴¹. This nutrient specific absorption can occur independently of body weight or epithelial hyperplasia. Lean animals have a greater ability to absorb glucose, fatty acids or amino acids if they are maintained on a diet that is high in each nutrient component^{42,43}. This increase in absorption, though, does not occur to the same extent as their obese, hyperphagic counterparts^{39,43,44}. This suggests that the amount *and* type of luminal nutrients may direct the function of enterocytes. It is not known, though, if this effect is induced directly on the mature epithelial cells or may be mediated through a nutrient-driven effect on the stem or progenitor cells earlier in their development.

3.2 Enteroendocrine cells

It may be expected that an increase in intestinal epithelial cell number would lead to an increase in cell responses, but that is not always the case. The increase in enteroendocrine cell number that occurs in obesity does not necessitate an increase in the hormones produced by these cells. For instance, nutrient induced increases in glucagon-like peptide-1 (GLP-1)

are attenuated in obese individuals compared with lean ^{45–47}. GLP-1 release from enteroendocrine L cells is known to be negatively regulated by uncoupling protein-2 (UCP-2; ^{48,49}). High levels of UCP-2 are found in obese animals and inhibition of UCP-2 results in an increase in GLP-1 ⁴⁸. Since the mature enteroendocrine cells are only functional for a few days before being replaced by new differentiated cells, it is not clear how differences in UCP-2 may be maintained across time in obese versus lean individuals.

Certainly diet interacts with all of the mature epithelial cells (*ie.* enterocytes, goblet cells, Paneth cells, enteroendocrine cells, M cells, Cup cells, tuft cells) and stimulates a host of cellular events that result in changes in digestion, absorption and hormone secretion. An increase in the absorption of nutrients or a decrease in nutrient-driven satiety hormone release are just examples of how intestinal epithelial adaptation may contribute to the maintenance of obesity. How the function of these cells is kept constant across generations of new cells is unknown, but may involve nutrient-induced changes in the mature epithelial cells or nutrient-induced determination earlier in development.

4. Nutrients are not the only driving force of intestinal adaptation

A clear understanding of the mechanisms that underlie diet-induced intestinal adaptation is confounded by the multitude of events that are initiated upon the ingestion of food and its contact with the intestinal epithelium. These events include, but are not limited to, changes in enzyme availability, bile acids, microbiota and immune factors. Altmann and Leblond ¹¹ revealed that such factors can drive intestinal adaptation. They took advantage of the anatomical difference in villus size along the proximal-distal axis of the intestine with villus height decreasing from the duodenum to the colon. They cut segments from portions of the intestine in rats and transplanted them to positions proximal or distal to the surgical site. When nutrients were free to flow, villus size increased in segments transplanted to proximal locations and decreased in more distal sites. In order to test if it was the nutrients or the pancreatic enzymes/bile secretions that mediate these changes, duodenal segments with and without the duodenal papilla were removed and connected to the colon at their distal end and sutured closed at their proximal end (leaving it free from nutrient flow). The villus size only in the duodenal segment with the papilla was the same as the pre-transplantation size. In contrast, the villus size of the duodenal segment without the papilla decreased. Taken together, it appears that the enzymes and bile from the duodenal papilla may drive increases in intestinal villi size, but factors in the distal intestine may promote decreases in size. Certainly diet affects various luminal contents, but these studies suggest that nutrients are not even necessary to see changes in intestinal morphology.

5. Conclusions and implications

Luminal nutrients are a driving factor in the alteration of intestinal morphology and function. The amount and specificity of the nutrients may even play greater roles than other factors associated with obesity. Understanding how nutrients interact with the epithelial cells to modulate cell proliferation, differentiation and the function of the mature cells will illuminate mechanisms in digestion, absorption and hormonal signaling. The increase in nutrient absorption or decrease in nutrient-induced satiety hormone release in obese

individuals could be attenuated if we could get their epithelial cells to function like that of lean individuals. This may be the first step needed to break that cycle of how nutrients are processed and stored in obesity.

Acknowledgments

This manuscript is based on work presented during the 2013 Annual Meeting for the Study of Ingestive Behavior, July 30-August 3, 2013. I thank Dr. Timothy Moran for his mentorship and support which served as a foundation for the work reviewed here. Supported by NIH grants DK-19302 (THM) and DK-092126 (MJD).

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Highlights

- There are differences in intestinal epithelial anatomy in lean and obese individuals
- The amount or type of nutrients may drive anatomical differences
- Nutrients may affect stem cells to alter proliferation or differentiation
- Epithelial differences result in altered nutrient processing

Figure 1.

Differences in intestinal morphology. A schematic representation of the crypt-villus structure in lean and obese individuals. Crypt stem cells, CBC/Lgr5 (gray) and +4/Bmi1 (black), continually generate new progenitor cells or transit amplifying (TA) cells. The TA cells divide as they migrate from the crypt to the villus. Differentiation of the TA cells into mature epithelial cell types occurs as the cells exit the crypt and enter into the villus. The goblet cells (oval), enteroendocrine cells (triangle) and enterocytes (rectangle) migrate to the tip of the villus, while the paneth cells (striped) migrate down to the crypt. As depicted, obese individuals have greater villi length, crypt depths and numbers of epithelial cells compared with lean.

Figure 2.

Nutrient-induced cell proliferation in the crypt. Nutrients or other secondary factors to diet may directly affect cell proliferation through the canonical Wnt/ β -catenin pathway in Lgr5 stem cells or progenitor cells. Glucose has been shown to increase β -catenin through cAMP/PKA pathway and increase β -catenin translocation to the nucleus in other stem cells (*see section 3.2*). Fatty acids have been shown to increase Wnt ligand availability (*see section 3.2*). Solid arrows indicate research has documented these signaling mechanism in other stem cell populations. Dashed arrows indicate that there is no current data to support a direct role of nutrients in cell proliferation in progenitor or Bmi1 cells.

Figure 3.

Nutrient-induced differentiation in the villi. Differentiation of the epithelial cells types from progenitor cells entails downstream components of Notch signaling. Hes1 activation results in enterocytes, Math1 activation results in goblet cells and ngn3 activation results in enteroendocrine cells. Dashed arrows indicate that it is unknown if nutrients drive changes in these mechanisms.