Physiology & Behavior 136 (2014) 74–78

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

Nutrient-induced intestinal adaption and its effect in obesity

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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.

ARTICLE INFO

Article history:
Received 30 November 2013
Received in revised form 18 February 2014
Accepted 25 March 2014
Available online 1 April 2014

Keywords:
Intestine
Adaptation
Stem cells
Diet
Obesity

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.

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1. Introduction

A myriad of differences in the morphology and function of the intestine have been documented between lean and obese individuals. The

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http://dx.doi.org/10.1016/j.physbeh.2014.03.026
0031-9384/

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], ob/ob [6,9] and db/db [10] mice, gold thioglucose [6]). Since Mayer and Yannoni [6] 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/transposition [11], hyperphagic animals models, such as lactation [12] or cold exposure [13,14]]. Whereas, the exclusion of luminal nutrients does the opposite [methods include: fasts [11], surgical bypass [15,16], hibernating animals [17], 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 composition [20]. 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 humans [21]. This process is characterized by the 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 are still unclear [22], 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 marker [23]. The other identified stem cell population which 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 marker [23]. 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 proliferation [23]. In contrast, the Bmi1 population is normally quiescent, becomes active after irradiation or injury and may not utilize Wnt signaling [23]. The Wnt/β-catenin signaling appears to be important in

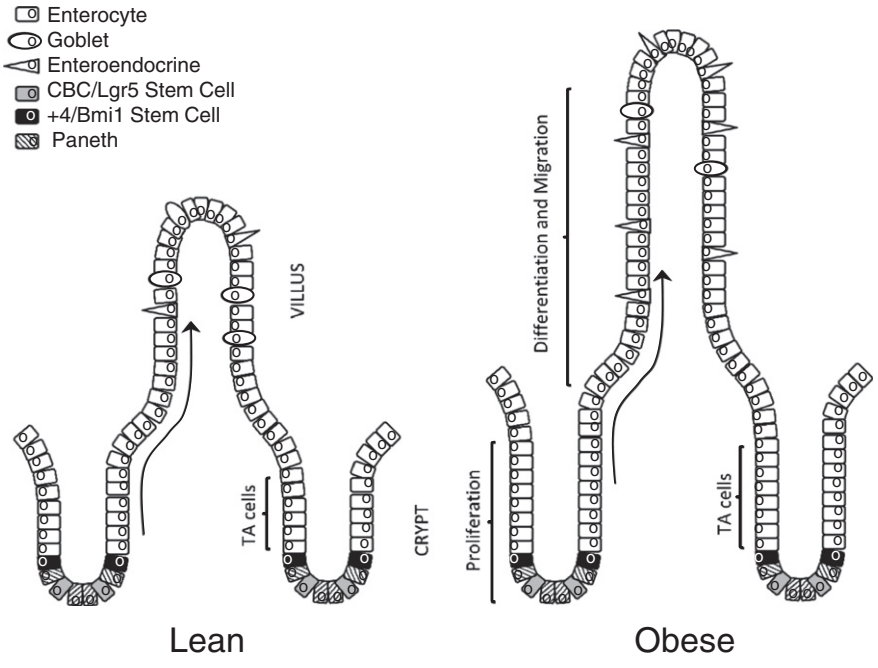

Fig. 1. Differences in intestinal morphology. A schematic representation of the crypt–villus structure in lean and obese individuals. Crypt stem cells, CBC/Lgr5 (gray) and +4/Bmi1 (black), continually generate new progenitor cells or transit amplifying (TA) cells. The TA cells divide as they migrate 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.