Keeping gut lining at bay: impact of emulsifiers

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Obesity is associated with altered gut microbiota and low-grade inflammation. Both dietary habits and food composition contribute to the onset of such diseases. Emulsifiers, compounds commonly used in a variety of foods, were shown to induce body weight gain, low-grade inflammation and metabolic disorders. These dietary compounds promote gut microbiota alteration and gut barrier dysfunction leading to negative metabolic alterations.

Obesity and metabolic disorders: the intestine as a gatekeeper

Obesity and related metabolic disorders (type-2 diabetes, liver and cardiovascular diseases) represent major public health problems that have reached pandemic proportions [1]. Importantly, excessive fat mass accumulation is associated with low-grade inflammation, which plays crucial role in the onset of obesity and related metabolic disorders. Unequivocal evidence suggests that low-grade inflammation originates through alterations of gut homeostasis. Obesity is associated with altered gut microbiota and gut barrier dysfunction, which are both involved in the development of pathology [2,3] and indeed, gut barrier function is compromised during obesity, diabetes and inflammation. Alterations, such as changes in the localization and distribution of the tight junction proteins, in the production of antimicrobial peptides, and in the composition of specific immune cells that infiltrate the gut mucosa, are involved in gut barrier dysfunctions [4-7]. Gut barrier function is also achieved through the presence of a mucus layer with sufficient thickness and specific composition capable of maintaining gut microbiota at distance from the gut [8] (Figure 1). Importantly, the reduction in mucus layer thickness reported during obesity participates in gut barrier dysfunction [5]. Changes in dietary habits and lifestyle are obviously involved in the increased incidence of obesity and metabolic disorders. However, revealing the existence of any dietary compounds responsible for deleterious effects on gut barrier function is of utmost interest, in this context.

Dietary emulsifiers shape the gut lining

Today, dietary emulsifiers such as carboxymethylcellulose (CMC) and polysorbate-80 (P80) are used in various foods at concentrations up to 2%. A recent study suggested that the growth in dietary emulsifier consumption over the past half century may contribute to a higher incidence of inflammatory bowel disease (IBD) and metabolic syndrome [9]. Indeed, consumption of two dietary emulsifiers (ranging from 0.1% to 1%) induces low-grade inflammation, fat mass development and metabolic disorders (i.e., glucose intolerance) [9]. The study also showed that both food additives are involved in the development of inflammation that resembles IBD as they promote chronic gut inflammation leading to robust colitis in mice lacking Toll-like receptor 5 (TLR5−/−), or Interleukin 10 (IL10−/−), two mouse models predisposed to developing intestinal inflammation [10]. More strikingly, in normal mice, the ingestion of low-dose emulsifiers promotes subtle signs of chronic intestinal inflammation including epithelial damage [9]. Such effects are associated with alterations in the gut microbiota composition and an increase in microbiota encroachment of the mucus. Importantly, the gut microbial community plays key role because transferring microbes from emulsifier-treated mice to germ-free mice that are not exposed to emulsifiers partially transmits metabolic syndrome.

Obesity and metabolic disorders: a question of energy balance

Obesity results from an imbalance between energy intake and energy expenditure; therefore, changes in food intake or in energy expenditure become important. Although emulsifiers induced gut barrier alterations and low-grade inflammation, they also resulted in significantly increased food intake (at least twice as high as the control mice). This is crucial, because increased food intake drives the development of obesity by increasing fat mass and promoting metabolic alterations. Food restriction experiments (i.e., pair-feeding) will help evaluate the contribution of increased food intake, whereby emulsifier treated mice received the same amount of food as untreated mice. This type of experiment can help decipher whether the impact of emulsifiers is mainly due to changes in food intake, or it extend beyond this. And if increased food intake is driving the obesity, then alternative mechanisms should be investigated in the future.

As the gut microbiota composition and the fecal short chain fatty acid (SCFA) profile are modified in emulsifier treated mice, such changes may also impact food intake. Growing evidence suggests that microbial products, for example butyrate and propionate, may directly bind to specific G-protein coupled receptors like GPR41/43 [3], enriched in enterodocrine L-cells. The stimulation of these receptors triggers the release of enterodocrine peptides, like glucagon-like peptide-1 (GLP-1) and peptide YY, that function in the gut/brain axis to reduce food intake. As butyrate has been reported to stimulate the
Dietary changes in the gut microbiota-host interactions (Figure 1) are important to investigate whether the observed decrease in butyrate observed upon dietary emulsifier consumption is associated with changes in enterocodendrine peptides, thereby explaining the increase in food intake (Figure 1).

An important point that warrants future investigation is the impact of dietary emulsifiers on the accessibility of specific nutrients to the gut bacteria. For instance, one may suggest that by impacting food intake, emulsifiers contribute to the modulation of energy sources in the gut, because increasing food intake also changes the flux of nutrients towards the gut lumen [11]. In addition, because emulsifiers are detergent-like molecules, we may not rule out that both CMC and P80 affect lipid absorption in the intestine, increasing lipid and bile acid flux into the gut lumen, thereby contributing not only to the modulation of the gut microbiota composition, but also gut inflammation (Figure 1).

Finally, changes in energy expenditure could also explain the emulsifier-induced alteration in gut microbiota, and the development of metabolic syndrome. Indeed, we recently discovered that changing gut microbe-host interactions (through intestinal deletion of MyD88, a molecule crucial for maintaining gut homeostasis) impacts the gut microbiota, gut barrier function, intestinal immunity, fat mass development and whole body energy expenditure [12].

Dietary emulsifiers: ‘a shield’ against the gut microbiota-host interactions?

Because germ free mice treated with dietary emulsifiers do not exhibit changes in food intake, fat mass or fasted glycemia, it is likely that gut microbiota-host interactions play key role, in this context. The gut and the gut microbiota constitute a complex ecosystem where both host cells and bacteria are literally conversing. By introducing emulsifiers in this system, it is possible that lipophilic compounds produced by the host or the bacteria are unable to reach their targets, hence altering the signaling between the gut microbes and the host, and thereby host metabolism. Thus, emulsifiers may influence the bacterial membrane and structure, directly impacting cellular replication and/or metabolism (Figure 1).

The question what are the effects of a putative daily exposure to such compounds, is still up for debate. Future studies are warranted to ascertain whether the overall population consuming such compounds is at risk. In addition, the potential weaknesses in the current knowledge and in the systems evaluating the safety of such dietary compounds come to the forefront.

In conclusion, although the molecular mechanisms and the exact human exposure levels to such compounds need to be investigated, the numerous metabolic parameters we discuss in this paper strongly support the need to better understand the key functions of gut microbiota, and their interactions with both food components and the host metabolism, in the context of obesity, low grade inflammation and diabetes.

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References

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Figure 1. Demonstrated and hypothesized mechanisms of action of emulsifiers on the gut lining. Emulsifiers change the mucus layer thickness and alter interactions between gut microbes and host cells. Putative additional mechanisms such as changes in the production of gut peptides involved in food intake, gut barrier function and glucose metabolism regulation warrant further investigation. The role of emulsifiers on antimicrobial peptide production as well as direct interactions with microbes may also occur in this context. Broken lines represent putative indirect or direct effects not yet established.