

METABOLISM

Dietary emulsifiers—sweepers of the gut lining?

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Refers to Chassaing, B. et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 519, 92–96 (2015)

Low doses of two commonly used dietary emulsifiers—carboxymethylcellulose and polysorbate-80—are reported to induce low-grade inflammation, metabolic disorders and increases in body weight in mice. These emulsifiers also promote colitis in mice that are susceptible to this disorder. Interestingly, changes in the gut microbiota were both necessary and sufficient to induce the metabolic alterations.

Obesity is characterized by a massive expansion of adipose tissue that is associated with the development of low-grade inflammation. Growing evidence suggests that this induction of inflammatory tone, which is observed in states of obesity and type 2 diabetes mellitus, might be initiated in the gut.¹ Unequivocal evidence has shown that under conditions of obesity and inflammation, maintenance of appropriate gut barrier function is crucial. Moreover, several factors, such as the localization and the distribution of tight junction proteins, production of antimicrobial peptides and presence of immune cells, as well as adequate mucus thickness and composition, have been implicated in the maintenance of this barrier function.^{2–5} Disturbance of any one of these mechanisms can contribute to the development of gut barrier dysfunction and, eventually, can lead to low-grade inflammation. Among the key factors, dietary composition, such as a high-fat diet or low fibre intake, contributes to the onset of diseases associated with leaky gut and the metabolic syndrome.^{3,6} Changing dietary habits, therefore,

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represents an easy way to avoid development of these disorders. As such, revealing the dietary products that exert these deleterious effects is of utmost importance. According to a new study, dietary emulsifiers might provide substantial contributions to development of metabolic disorders.⁷

In an elegant series of experiments, Chassaing and colleagues showed that chronic ingestion of two commonly used dietary emulsifiers, carboxymethylcellulose and polysorbate-80, by wild-type mice results in alterations to the mucus barrier, induction of low-grade inflammation, increases in levels of body fat and development of metabolic disorders.⁶ These effects were observed in strains of mice that were either prone or resistant to obesity. Strikingly, ingestion of low-dose emulsifiers promoted marked signs of colitis in *Tlr5*^{-/-} mice and *Il10*^{-/-} mice, which are two models of this disease with increased susceptibility to intestinal inflammation and changes in gut microbial composition.⁸ By contrast, ingestion of emulsifiers did not induce overt colitis in wild-type mice, despite observations of subtle histological changes and evidence of chronic inflammation, including signs of epithelial damage, in these animals.⁶ Thus, emulsifiers seem to promote degradation of the mucus lining, which contributes

to robust development of colitis in susceptible host animals and induction of low-grade inflammation and metabolic disorders in wild-type mice.

Chassaing and co-workers also clearly demonstrated that the induction of low-grade inflammation and obesity by emulsifiers requires the presence of gut microbes; germ-free animals were resistant to the onset of these diseases.⁷ Previous studies have identified putative pathobionts that are involved in metabolic disorders; abundance of the genus *Bilophila* is increased in *Il10*^{-/-} mice, which have increased susceptibility to colitis when fed a high-fat diet.⁸ Interestingly, the increased abundance of this genus has also been associated with a high-fat diet and intestinal barrier dysfunction, whereas treatment with prebiotics mitigated this effect in mice.^{6,9} Thus, *Bilophila*-derived metabolites might serve as breakers of the mucosal barrier, which enables infiltration of immune cells and induction of inflammation in the gut.^{6,9}

Given that *Bilophila* spp. are resistant to bile acids, it is probable that the increased abundance of this genus results from changes in bile acid flux induced by ingestion of emulsifiers. In accordance with this hypothesis, in this new study, the bile acid profiles of conventional mice were altered,⁷ which could either influence or be influenced by the composition of the gut microbiota. Chassaing and colleagues exclude a purely direct role of the emulsifiers on bile acids and mucus, as germ-free mice did not exhibit changes in mucus thickness or bile acid profiles. However, in germ-free mice, bile acid metabolism is, by essence, compromised; therefore, these mice might not represent an adequate model in which to address this specific question.

The modulation of bile acid flux that is observed in conventional mice might result from changes in reabsorption because emulsifiers can change the structure of micelles in the gut, which, in turn, could affect gut microbes—an effect which might not be detected in germ-free mice. These data strongly suggest that both carboxymethylcellulose and polysorbate-80 modulate the gut microbiota by changing its activity and composition. Another mechanism that could be interesting to investigate



is the role of emulsifiers in altering production of antimicrobial peptides and the infiltration of immune cells into the gut. Given the data presented in this new study with regard to changes in gut microbiota composition, mucus layer thickness and levels of short-chain fatty acids and bile acids, it would be expected that emulsifiers could also have effects on production of antimicrobial peptides and/or the immune infiltrate. Moreover, this assertion is supported by data that have shown an important relationship between the microbiota and the immune infiltrate in both colitis and obesity.^{3–6}

Emulsifiers are generally recognized as safe by the FDA and are used in various processed foods at levels of up to 2%.⁷ Notably, in the current study, the authors assessed different doses of carboxymethylcellulose and polysorbate-80 and found effects on host adiposity and intestinal morphology at concentrations as low as 0.1%. In addition, carboxymethylcellulose consumption was shown to have long-lasting negative effects, such as increased adiposity and myeloperoxidase activity in the intestine, whereas the deleterious effects of polysorbate-80 were reversible.

But, the question remains: is the broad use of emulsifying agents in food products responsible for the contemporary pandemic obesity and inflammatory diseases? Probably not. The study was performed in rodents receiving chronic doses of the additives in their drinking water and/or diet, which resulted in levels of these compounds reaching at least 0.1% to 1.0% of the total amount of food ingested per 24 h.⁷ To directly translate these results to humans on the basis of these findings, we would assume that all food items ingested throughout the day contain from 0.1% to 2.0% of emulsifiers, which

is probably an overestimation. However, increased daily exposure to emulsifiers might not be excluded in some populations, according to their dietary habits. Even so, the study has enough merit to highlight an additional potential weakness in the system that evaluates the safety of additive compounds used in modern diets.¹⁰ Moreover, we should not dismiss the idea that the multiple exposures and combinations of similar compounds might worsen some metabolic parameters in individuals who have increased sensitivity, or might be predisposed, to the onset of metabolic diseases.

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In conclusion, additional studies investigating the exact levels of exposures to these compounds in humans, as well as the mechanisms and the effects on obesity, low-grade inflammation and the microbiota, are warranted. Without this additional data, we cannot completely refute the contributions of such environmental factors to the onset of colitis and other metabolic disorders.

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Competing interests

The author declares no competing interests.

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