Published in final edited form as:
Ann Allergy Asthma Immunol. 2014 April ; 112(4): 296–301. doi:10.1016/j.anai.2013.08.002.

Stress and food allergy: mechanistic considerations

Hannah M.C. Schreier, PhD and **Rosalind J. Wright, MD, MPH**
Department of Pediatrics, Icahn School of Medicine, New York, New York

Abstract

Recent years have seen a marked increase in food allergy prevalence among children, particularly in Western countries, that cannot be explained by genetic factors alone. This has resulted in an increased effort to identify environmental risk factors underlying food allergies and to understand how these factors may be modified through interventions. Food allergy is an immune-mediated adverse reaction to food. Consequently, considerations of candidate risk factors have begun to focus on environmental influences that perturb the healthy development of the emerging immune system during critical periods of development (eg, prenatally and during early childhood), particularly in the gut. Given that psychosocial stress is known to play an important role in other allergic and inflammatory diseases, such as asthma, its potential role in food allergy is a growing area of research. However, research to date has largely focused on animal studies. This review synthesizes relevant animal research and epidemiological data, providing proof of concept for moderating influences of psychological stress on food allergy outcomes in humans. Pathways that may underlie associations between psychosocial stress and the expression of food allergy are discussed.

Introduction

Recent years have seen a marked increase in food allergy prevalence in children, particularly in Western countries.[1] The prevalence of food allergy peaks in the first few years of life.[2] Estimates from a large nationally representative sample of US households have suggested that currently up to 8% of American children have food allergies.[3] Notably, close to 40% of children with food allergies have been reported to have had severe allergic reactions in the past and multiple food allergies are common.

It is generally accepted that food allergies have increased in prevalence at a rate beyond what can be explained by genetic factors. Consequently, there has been an increased effort in recent years to identify environmental risk factors underlying food allergies and to understand how these factors might be modified through interventions. Food allergy is an immune-mediated adverse reaction to food. Thus, considerations of candidate risk factors have begun to focus on environmental influences that disrupt the healthy development of the emerging immune system during critical periods of development (eg, prenatally, during

Reprints: Rosalind J. Wright, MD, MPH, Department of Pediatrics, Icahn School of Medicine, Box 1198, New York, NY 10029; rosalind.wright@mssm.edu.

Disclosures: Authors have nothing to disclose.

early childhood), particularly in the gut. Because psychosocial stress plays an important role in other allergic and inflammatory diseases, such as asthma,[4] its potential role in food allergy is a growing area of research. However, research to date has largely focused on animal studies.

The present review synthesizes relevant animal research and epidemiologic data, providing proof of concept for the moderating influences of psychological stress on food allergy in humans. The reviewers submit that psychosocial stressors can affect food allergy outcomes similarly to the way in which psychosocial stressors have been shown to affect asthma outcomes and will outline some potential physiologic pathways that may be involved.

Background

Food allergies are particularly common in young children younger than 2 years and then decrease in prevalence as children age and at times “outgrow” their allergies.[5] Research has indicated that the vast majority of food allergies (~90%) can be attributed to a small number of food items, including milk, egg, soy, wheat, fish and shellfish, and peanut and tree nuts.[5] However, many gaps remain in understanding the epidemiology of food allergy and the environmental factors that contribute to population-based patterns.

It is important to differentiate between food intolerance and food hypersensitivities (ie, allergies).[5] The former represents a nonimmune-mediated physiologic response to the ingestion of food resulting from contaminants in food. In contrast, food allergies are the result of both immunoglobulin E (IgE)-mediated and non–IgE-mediated immune mechanisms. Most IgE-mediated reactions occur more readily, typically within 1 to 2 hours of ingestion, and most food allergy symptoms can affect the gastrointestinal and respiratory tracts, skin, and systemic circulation.[5] However, most people do not develop clinical symptoms after the ingestion of most foods because they have developed oral tolerance, characterized by T-cell anergy and the production of regulatory cytokines and antigen-specific IgA antibodies.[5]

For systemic clinical symptoms to occur, food allergens must first cross from the lumen through the epithelial barrier to the intestinal mucosa.[6] Even in healthy individuals with an intact gut barrier, a small percentage of food antigens crosses the epithelial barrier, allowing for potential adverse reactions to such foods. During IgE-mediated reactions, allergens crossing the epithelial barrier then bind to IgE found on mast cells, causing them to degranulate and release allergic mediators, such as histamines. Conversely, non–IgE-mediated reactions are less well understood but likely involve antigens being presented to T cells in the intestinal mucosa. These in turn release cytokines that can lead to long-term changes to epithelial cells and the intestinal mucosa.[7]

It has become clear that the epithelial barrier plays an important role in the development and maintenance of oral tolerance, because the mucosal barrier must learn to differentiate between potentially harmful pathogens and benign food antigens. Dendritic cells also play a key role in the development of oral tolerance.[8] One type of dendritic cell is responsible for presenting antigens to T cells; another type, located in Peyer patches in the intestinal mucosa, aids by expressing interleukin (IL)-10 and IL-4. Additional factors, such as the

composition of the gut flora and the generation of T regulatory cells in response to low-dose antigen exposure, are other important contributors to the development of tolerance.[9]

Psychosocial Stress and Food Allergy

Although numerous studies have focused on the wide-ranging psychological impact that food allergies have on children and their families,[10] ranging from greater perceived stress to higher rates of anxiety disorders, the influence of psychosocial factors, such as stress, on food allergy development has been largely ignored until recently.

Evidence From Animal Research

Increasingly, findings based on animal research have suggested that experiencing psychological stress can affect and disrupt physiologic processes thought to be central to clinical manifestations of food allergy. Most of these studies have focused on rodent models and explored the influences of stress on intestinal barrier functioning, inflammation in the intestine, and the microbiota.

Intestinal barrier functioning

Rodent models have provided convincing evidence of acute and chronic stress exposures altering intestinal barrier functioning. Studies have shown that acute stress, typically in the form of restraint stress, increases epithelial permeability in the rat intestine,[11] resulting in greater ion secretion[12] and macromolecular uptake across the epithelium, eg, of commonly used model proteins, such as horseradish peroxidase,[13] compared with non-stressed control rats. Additional data have suggested that the increased epithelial permeability after acute stress exposure may be due at least in part to an increased release of peripheral corticotropin-releasing hormone (CRH).[14,15]

Studies exposing rats to chronic stress, eg, chronic water avoidance stress[16] or chronic crowding stress,[17,18] have reached similar conclusions, suggesting that stress exposure increases epithelial permeability and ion secretion, and CRH has been implicated as a potential mediator.[17] Stress exposure during early life has been of particular interest and is among the most popular models for investigating the influence of chronic stress on intestinal outcomes through what has been termed the *brain–gut axis*.[19,20] Studies comparing rat pups exposed to maternal separation after birth with control pups that were not separated from their dams have shown that separated pups show evidence of increased colonic permeability and subsequent bacterial translocation[21] and a greater immune response to induced colitis.[22]

Multiple potential mediating pathways have been implicated in this process, such as the involvement of peripheral CRH,[21,23] which may influence the epithelial barrier by stimulating cholinergic nerves.[24] Much evidence has suggested the involvement of mast cells in epithelial barrier function. Chronic crowding[25] and a rat model of stress-induced depression[26] have been associated with greater mast cell proliferation and degranulation. Of interest, Chen et al[26] found that administration of fluoxetine, an antidepressant, prevented the effects of chronic stress on mast cells in the gastric antrum. These findings are supported by 2 studies that reported that mast cell–deficient rats subjected to water avoidance stress did not exhibit the same changes, ie, greater ion secretion and epithelial permeability, as

stressed wild-type rats.[27,28] Additional pathways may include increased nerve growth factor release in the rat brain,[29] supporting the idea of the brain–gut axis, and a generally altered distribution of secretory cells in the intestinal epithelium, featuring fewer Paneth and goblet cells (these are contributing factors to the epithelial barrier) and an increase in endocrine cells.[30]

Together these studies outline the role of psychosocial stressors on epithelial permeability in the gut and suggest that exposure to psychosocial stressors may increase the transepithelial passage of food antigens into the intestinal mucosa, thereby increasing the risk of adverse reactions to these foods.

Intestinal inflammation

Fewer studies have used rat models of chronic stress to investigate the impact on inflammatory processes in the gut. However, existing studies have suggested that being subjected to chronic stress shifts the intestinal mucosa toward a more inflammatory state. For example, Yang et al[16] reported that chronic water avoidance stress led to rats exhibiting a more allergic profile marked by increased IL-4 and decreased interferon-γ in the intestinal mucosa. These findings are supported by other studies that have found that exposure to conditions of chronic crowding results in greater myeloperoxidase activity, indicative of neutrophil infiltration, and a greater than 10 times larger number of total leukocytes in the rat lumen.[17,25] Further in line with these studies have been findings suggesting that early life exposure to maternal deprivation can lead to increased inflammatory profiles in the rat intestine. O'Mahony et al[31] found that rats exposed to maternal deprivation showed increases in tumor necrosis factor-α and interferon-γ, although not in IL-6, IL-4, and IL-10, compared with control rats. Similarly, maternal deprivation has been linked to increased mRNA expression of numerous cytokines, including interferon-γ, IL-1B, IL-2, IL-4, and IL-10 in the rat colon, liver, and spleen.[22] Importantly, this last study assessed cytokine mRNA expression when rats were 12 weeks old, indicating that chronic stress exposure during early life can have potentially long-lasting effects on the gut inflammatory state. Hence, individuals at risk for food allergies may be particularly susceptible to developing clinical symptoms after ingestion during times of stress, because stress exposure may push them toward a more inflammatory intestinal profile.

Another likely important moderating factor in intestinal inflammation that has received insufficient attention is autonomic balance. The autonomic nervous system becomes activated during stress[32] and is involved in the regulation of proinflammatory cytokines by the release of epinephrine and norepinephrine through efferent vagus nerve fibers that innervate the intestine; this is called the *cholinergic anti-inflammatory pathway*.[33,34] Animal research has shown that electrical stimulation of the vagus nerve results in decreased intestinal inflammation, whereas surgical removal of the vagus nerve leads to increased inflammation.[35,36]

Using a rat model of induced colitis, Saunders et al[37] found that cholinergic neural pathways are likely involved in inflammatory relapse after a non-colitic dinitrobenzene sulfonic acid dose and restraint stress. However, they assessed only cardiac sympathovagal balance in this study. Evidence from mice models has suggested further the vagus nerve can have a

protective effect against acute colitis relapses in the presence of ongoing intestinal inflammation[38] and that efferent vagus nerve fibers in the intestine may contribute to a skewed T-helper type 2 (T_H2) profile by influencing dendritic cell phenotypes in the intestine.[39] Of particular interest is a study by Ghia et al[40] who studied a murine model of depressive-type behaviors. These behaviors resulted in an increased susceptibility to intestinal inflammation by altering the regular tonic vagal inhibition of proinflammatory factors, such as macrophages. These effects were reversed at administration of tricyclic antidepressants. These results are highly suggestive of autonomic contributions to intestinal inflammation and of the idea that these contributions can be influenced by psychosocial stress.

Intestinal microbiota

The intestinal microbiota is increasingly being viewed as an important mechanism in allergic disease.[41] Germ-free mice have been found to be more susceptible to cow milk allergy,[42] suggesting that the microbiota may play a protective role in allergy susceptibility. This is supported further by a follow-up study using gnotobiotic mice to show that a transplanted healthy infant microbiota was protective of sensitization and food allergy.[43] Research comparing Toll-like receptor 4 mutant or deficient mice with control mice has shown that the intestinal commensal flora can inhibit allergic responses to food allergens through Toll-like receptor 4 signaling[44]; similarly, commensal bacteria introduced to germ-free mice influenced gene expression, which in turn altered mucosal barrier fortification and nutrient absorption.[45] Noval Rivas et al[46] suggested that mice prone to food allergy have a particular gut microbiota that puts them at risk. They compared wild-type with allergy-prone mice that had been orally sensitized with chicken egg ovalbumin and found that the microbiota signature of allergy-prone mice, but not wild-type mice, was marked by an excess of bacterial families.

Some studies have suggested that the gut microbiota can be influenced by exposure to psychosocial stressors. Mice deprived of food, water, and bedding for 48 hours had a gut microbiota marked by more bacterial families and fewer lactobacilli compared with nonstressed control mice.[47] Relatedly, early life maternal deprivation in rats has been shown to result in a significantly altered microbiota signature compared with control rats.[31] Perhaps most intriguingly, 2 studies have investigated the influence of maternal prenatal stress exposure and early life stress on intestinal microbiota composition in infant rhesus monkeys. Offspring of rhesus monkeys that had been stressed using an acoustic startle paradigm for 6 weeks late or early during their pregnancy had smaller numbers of bifidobacteria and lactobacilli in their gut microbiota.[48] Prenatal maternal separation yielded similar results. However, the decrease in lactobacilli in the gut microbiota was accompanied by more stress-indicative behaviors among the infant monkeys and greater susceptibility to opportunistic bacterial infection.[49]

As that study implies, there is some evidence showing that the gut microbiota can influence behavior and stress-response systems. For example, germ-free mice exhibited anxiolytic behavior in the elevated plus maze compared with specific-pathogen–free mice[50] and showed an exaggerated hypothalamic–pituitary–adrenal response after restraint stress.[51]

These data suggest that the experience of stressors can alter the makeup of the gut microbiota and that this in turn may have important effects on behavior and stress responses.

The beneficial effects of a probiotic diet also are being seen.[52] Although not all probiotic strains may be equally beneficial, data showing benefits of probiotic diets are beginning to accumulate. Specifically, probiotics have been shown to restore and ameliorate gut permeability and bacterial penetration after stress exposure[53,54] and to prevent an increase in gut permeability and bacterial adhesion and translocation in animals pretreated with probiotics.[11,18]

Evidence From Human Research

Data evaluating the impact of psychosocial stressors on food allergy–related outcomes in humans are sparse compared with the relatively comprehensive animal literature. One study found that young children who relocated to an international location with their family were at an increased risk of allergic sensitization a year later compared with control participants who did not move, but this study did not focus specifically on outcomes relevant to food allergies and no potential underlying physiologic mechanisms were evaluated.[55] Nonetheless, the few studies that do exist have pointed to interesting parallels between animal and human studies.

Intestinal barrier functioning

Some evidence has suggested that mechanisms similar to those identified in animals may be operating in humans and connected the experience of psychosocial stress to altered intestinal permeability. For example, a CRH pathway linking stress to intestinal permeability may exist in humans. It is well known that stress exposure influences the hypothalamic–pituitary–adrenal axis, at the heart of which lies CRH production in the hypothalamus.[56] In vitro CRH challenges to colon biopsies taken from healthy human participants have shown that this results in an increased uptake of horseradish peroxidase, likely by acting on mast cells to increase intestinal permeability, similar to findings from research using rodent models described earlier.[57,58]

Two studies have investigated the effect of acute and chronic stresses on epithelial permeability in the intestine in human participants. Santos et al[59] investigated the response to cold pain–induced stress in healthy vs food-allergic participants. Closed segment perfusion of the jejunum showed that in the healthy and food-allergic participants, luminal release of mast cell mediators increased after the cold pain stressor. However, food-allergic participants showed a greater increase of tryptase and histamine compared with healthy participants and only in the food-allergic group did these changes resemble those observed after an antigen-challenge. This indicates that stress exposure results in changes at the intestinal level that puts food-allergic patients at an increased risk of developing clinical allergic symptoms. A similar association may exist for chronic stress. Alonso et al[60] compared healthy women with low vs moderate “background,” ie, chronic life stress. Jejunal segment perfusion after cold pain stress showed that women who had previously reported moderate chronic stress showed a greater increase of albumin permeability than women who had reported low chronic stress. However, these findings will need to be replicated in

women with food allergies. In addition, these studies had small samples and should be replicated in larger samples.

Intestinal inflammation

Almost no human studies have investigated the relation between psychological stress and intestinal inflammation in the context of food allergies. However, data from patients with inflammatory bowel syndrome have suggested that experiencing psychosocial stressors may increase inflammation in the gut, because it is often associated with worsened clinical outcomes and slower recovery.[61] For example, Bennett et al[62] prospectively followed patients with inflammatory bowel syndrome over 16 months. Chronic life stress experienced during the 6 months leading up to assessment was a strong predictor of symptom intensity over the subsequent 16 months, such that only patients not exposed to chronic stressors showed clinical improvement over the follow-up period. However, symptom intensity and life stressors were assessed using self-report only and intestinal inflammation was not assessed directly.

Evidence for the potential damaging effect of acute stress comes from a study that investigated intestinal inflammation after stress exposure in patients with inactive ulcerative colitis and healthy control participants.[63] Participants were exposed to a psychological stressor, the administration of an IQ test under time pressure and additional auditory distractions, and underwent peripheral blood draws, rectal biopsies, and perimucosal fluid collection before and after the stressor. Results showed that acute stress can lead to an increase in tumor necrosis factor-α in rectal perimucosal fluid (although no change was seen in IL-13 and histamine levels). These changes were evident in patients with ulcerative colitis and healthy participants. In addition, biopsy results suggested that in all participants with some inflammation noticeable before stressor administration, inflammation increased after the stressor. Hence, these results provide some initial support for the idea that acute and chronic stress exposures may increase intestinal inflammation in humans, with potentially more detrimental consequences for those at risk for inflammatory or allergic diseases.

Although there is a shortage of empirical studies evaluating the connection between psychosocial stressors and intestinal inflammation, the physiologic mechanisms that likely underlie this process are relatively well understood. Food allergies are marked by a shift toward T_H2 cytokine production. Psychosocial stress leads to the release of CRH in the hypothalamus and in numerous local tissues[64]; this in turn may result in increased mast cell degranulation, underscoring the important role of mast cells in this process.[65]

Two human studies have pointed to the potential importance of autonomic balance with respect to intestinal inflammation. Initial evidence has linked psychosocial stress to autonomic balance and, in turn, autonomic balance to intestinal inflammation. For example, although they were able to assess only cardiac autonomic nervous system activity, Pieper et al[66] found that during episodes of worry, participants exhibited an increased heart rate. One study assessed the effect of psychosocial stress on gastric autonomic nervous system activity.[67] Participants' postprandial gastric myoelectrical and vagal activities (heart rate variability) were assessed at baseline, after a relaxation exercise, and after a stressful stimulus (a horror movie). Although there were no differences between the control and

relaxation conditions, results showed that after exposure to a horror movie, the increase in postprandial myoelectrical activity was lower, as measured by the percentage of normal slow waves, as was the increase in postprandial heart rate variability. Additional factors may be important to consider. Humans alter their food intake when experiencing psychosocial stressors and make less healthy food choices.[68] This in turn may alter the information carried from the gut back to the brain, further influencing associations among psychosocial stress, autonomic balance, and inflammation.[69]

Intestinal microbiota

Many studies have evaluated the importance of the intestinal microbiota in humans, although the direct connection between exposure to stressors and altered microbiota as it relates to food allergies remains unexplored.

Colonization of the gut typically begins at birth, although it is influenced by several factors, such as method of delivery. Data from a population-based Norwegian cohort suggested that in children with a parental history of allergy, delivery by cesarean section increased the risk of developing food allergies over the subsequent 2.5 years, likely because children did not come in contact with maternal vaginal microflora during delivery.[70] Furthermore, another study of a large sample showed that the makeup of the maternal vaginal microflora during pregnancy predicts wheeze and asthma risk in 5-year-old children.[71]

Multiple studies have linked the infant intestinal microbiota to atopic diseases and allergy.[72] Two studies, although with small samples, have suggested that the infant microbiota may have a greater influence on the development of eczema than of wheeze. Abrahamsson et al[73] found that, compared with control infants, infants with atopic eczema at 2 years of age had a lower diversity of total microbiota, marked by lower levels of the bacterial genus *Bacteroides* species in their stool samples when they were 1 month old. This is in line with findings from another study suggesting that, although there was no difference between wheezy and nonwheezy children with respect to their intestinal microbiota at 4 years of age, children with eczema had fewer bifidobacteria in their stool samples.[74] Interestingly, data from a randomized controlled trial indicated that administration of probiotics to mothers during pregnancy lowered the risk for atopic eczema in their children during the first 4 years of life compared with infants of mothers who received placebo capsules.[75]

With respect to food allergies specifically, research has indicated that, compared with healthy infants, those who are allergic to cow milk protein show evidence of dysbiosis, ie, microbial imbalance in the gut.[76,77] Maternal breast milk may be a contributing factor, because breast milk samples of mothers who had allergic diseases contained lower levels of bifidobacteria, which in turn was associated with lower levels of the same in their infants' stool samples.[78]

These studies provide convincing evidence that the intestinal microbiota plays an important role in the development of food allergies. However, the role of psychosocial stress exposure in this process has yet to be investigated. As discussed in the previous section, exposure to stress may accentuate the T_H1/T_H2 imbalance, inducing a greater shift toward a T_H2 profile. Research has suggested that a healthy microbiota may result in greater T regulatory cell and

T_H1 cell differentiation,[79] which would provide a necessary balance to stress-induced T_H2 proliferation. Hence, dysbiosis may increase the risk of developing allergic reactions to certain foods.

Conclusion

Food allergies are increasing and represent a significant problem that affects many individuals, in particular children and youth. Although some physiologic mechanisms underlying clinical food allergy symptoms are relatively well understood, almost no research has examined the influence of psychosocial stress exposure on food allergy outcomes in humans.

Numerous studies using animal models have provided intriguing evidence suggesting that exposure to acute and chronic stresses can affect aspects thought to be involved in the development of food allergies, including epithelial permeability in the gut, intestinal inflammation, and the makeup of the intestinal microbiota. However, although there is evidence to suggest that similar mechanisms are at play in humans, empirical evidence supporting these connections is missing.

Evidence from other disease models, such as asthma,[4] has shown that stressful experiences can have effects on the development and maintenance of chronic disorders. This is of interest with respect to food allergy, especially in light of the observation that many individuals are sensitized to particular foods yet fail to show overt clinical symptoms. This raises the question of whether psychological stress exposure may be one factor that plays a role in moderating physiologic responses to food ingestion in the presence of sensitization.

Future research should focus on establishing a direct link between stress exposure and clinical food allergy symptoms in humans; subsequent studies should focus on investigating in more detail the mechanisms underlying this connection in humans. To date, most studies that have focused on intestinal permeability and inflammation have used very small samples, undoubtedly because of the invasive nature of this type of study and the relatively high participant burden. Nonetheless, future studies should aim to take advantage of larger, more representative, samples as this important issue continues to be investigated. In its current state, generalizing from existing research to the larger population remains difficult. Understanding the connections between psychosocial stress exposure and food allergy outcomes may lead to the development of valuable intervention work in the future, ultimately decreasing the burden of food allergy on youth.

References

[1]. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009; 124:1549–1555. [PubMed: 19917585]

[2]. Berin MC, Sampson HA. Food allergy: an enigmatic epidemic. Trends Immunol. 2013; 8:390–397. [PubMed: 23648309]

[3]. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011; 128:e9–e17. [PubMed: 21690110]

[4]. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. Curr Opin Allergy Clin Immunol. 2005; 5:23–29. [PubMed: 15643340]

[5]. Sampson HA. Food allergy. J Allergy Clin Immunol. 2003; 111:S540–S547. 9. suppl. [PubMed: 12592300]

[6]. Kim JS, Sampson HA. Food allergy: a glimpse into the inner workings of gut immunology. Curr Opin Gastroenterol. 2012; 28:99–103. [PubMed: 22134223]

[7]. Jyonouchi H. Non-IgE mediated food allergy. Inflamm Allergy Drug Targets. 2008; 7:173–180. [PubMed: 18782024]

[8]. Ruiter B, Shreffler WG. The role of dendritic cells in food allergy. J Allergy Clin Immunol. 2012; 129:921–928. [PubMed: 22464669]

[9]. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol. 2010; 125:S116–S125. [PubMed: 20042231]

[10]. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy. 2010; 65:933–945. [PubMed: 20180792]

[11]. Agostini S, Goubern M, Tondereau V, et al. A marketed fermented dairy product containing Bifidobacterium lactis CNCM I-2494 suppresses gut hypersensitivity and colonic barrier disruption induced by acute stress in rats. Neurogastroenterol Motil. 2012; 24:376–e172. [PubMed: 22272920]

[12]. Saunders PR, Kosecka U, McKay DM, Perdue MH. Acute stressors stimulate ion secretion and increase epithelial permeability in rat intestine. Am J Physiol Gastrointest Liver Physiol. 1994; 267:G794–G799.

[13]. Kiliaan AJ, Saunders PR, Bijlsma PB, et al. Stress stimulates transepithelial macromolecular uptake in rat jejunum. Am J Physiol Gastrointest Liver Physiol. 1998; 275:G1037–G1044.

[14]. Santos J, Saunders PR, Hanssen NP, et al. Corticotropin-releasing hormone mimics stress-induced colonic epithelial pathophysiology in the rat. Am J Physiol Gastrointest Liver Physiol. 1999; 277:G391–G399.

[15]. Saunders PR, Santos J, Hanssen NP, Yates D, Groot JA, Perdue MH. Physical and psychological stress in rats enhances colonic epithelial permeability via peripheral CRH. Dig Dis Sci. 2002; 47:208–215. [PubMed: 11852879]

[16]. Yang PC, Jury J, Soderholm JD, Sherman PM, McKay DM, Perdue MH. Chronic psychological stress in rats induces intestinal sensitization to luminal antigens. Am J Pathol. 2006; 168:104–114. quiz 363. [PubMed: 16400013]

[17]. Vicario M, Alonso C, Guilarte M, et al. Chronic psychosocial stress induces reversible mitochondrial damage and corticotropin-releasing factor receptor type-1 upregulation in the rat intestine and IBS-like gut dysfunction. Psychoneuroendocrinology. 2012; 37:65–77. [PubMed: 21641728]

[18]. Zareie M, Johnson-Henry K, Jury J, et al. Probiotics prevent bacterial trans-location and improve intestinal barrier function in rats following chronic psychological stress. Gut. 2006; 55:1553–1560. [PubMed: 16638791]

[19]. Cryan JF, O'Mahony SM. The microbiome–gut–brain axis: from bowel to behavior. Neurogastroenterol Motil. 2011; 23:187–192. [PubMed: 21303428]

[20]. O'Mahony SM, Hyland NP, Dinan TG, Cryan JF. Maternal separation as a model of brain–gut axis dysfunction. Psychopharmacology (Berl). 2011; 214:71–88. [PubMed: 20886335]

[21]. Gareau MG, Jury J, Yang PC, MacQueen G, Perdue MH. Neonatal maternal separation causes colonic dysfunction in rat pups including impaired host resistance. Pediatr Res. 2006; 59:83–88. [PubMed: 16326990]

[22]. Barreau F, Ferrier L, Fioramonti J, Bueno L. Neonatal maternal deprivation triggers long term alterations in colonic epithelial barrier and mucosal immunity in rats. Gut. 2004; 53:501–506. [PubMed: 15016743]

[23]. Barreau F, Cartier C, Leveque M, et al. Pathways involved in gut mucosal barrier dysfunction induced in adult rats by maternal deprivation: corticotrophin-releasing factor and nerve growth factor interplay. J Physiol. 2007; 580:347–356. [PubMed: 17234701]

[24]. Gareau MG, Jury J, Perdue MH. Neonatal maternal separation of rat pups results in abnormal cholinergic regulation of epithelial permeability. Am J Physiol Gastrointest Liver Physiol. 2007; 293:G198–G203. [PubMed: 17510196]

[25]. Vicario M, Guilarte M, Alonso C, et al. Chronological assessment of mast cell-mediated gut dysfunction and mucosal inflammation in a rat model of chronic psychosocial stress. Brain Behav Immun. 2010; 24:1166–1175. [PubMed: 20600818]

[26]. Chen ZH, Xiao L, Chen JH, et al. Effects of fluoxetine on mast cell morphology and protease-1 expression in gastric antrum in a rat model of depression. World J Gastroenterol. 2008; 14:6993–6998. [PubMed: 19058337]

[27]. Santos J, Benjamin M, Yang PC, Prior T, Perdue MH. Chronic stress impairs rat growth and jejunal epithelial barrier function: role of mast cells. Am J Physiol Gastrointest Liver Physiol. 2000; 278:G847–G854. [PubMed: 10859213]

[28]. Soderholm JD, Yang PC, Ceponis P, et al. Chronic stress induces mast cell–dependent bacterial adherence and initiates mucosal inflammation in rat intestine. Gastroenterology. 2002; 123:1099–1108. [PubMed: 12360472]

[29]. Barreau F, Cartier C, Ferrier L, Fioramonti J, Bueno L. Nerve growth factor mediates alterations of colonic sensitivity and mucosal barrier induced by neonatal stress in rats. Gastroenterology. 2004; 127:524–534. [PubMed: 15300585]

[30]. Estienne M, Claustre J, Clain-Gardechaux G, et al. Maternal deprivation alters epithelial secretory cell lineages in rat duodenum: role of CRF-related peptides. Gut. 2010; 59:744–751. [PubMed: 20551459]

[31]. O'Mahony SM, Marchesi JR, Scully P, et al. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. Biol Psychiatry. 2009; 65:263–267. [PubMed: 18723164]

[32]. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun. 2007; 21:901–912. [PubMed: 17475444]

[33]. Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. Brain Behav Immun. 2005; 19:493–499. [PubMed: 15922555]

[34]. Teff KL. Visceral nerves: vagal and sympathetic innervation. JPEN J Parenter Enteral Nutr. 2008; 32:569–571. [PubMed: 18753395]

[35]. de Jonge WJ, van der Zanden EP, The FO, et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nat Immunol. 2005; 6:844–851. [PubMed: 16025117]

[36]. Matteoli G, Boeckxstaens GE. The vagal innervation of the gut and immune homeostasis. Gut. 2012

[37]. Saunders PR, Miceli P, Vallance BA, et al. Noradrenergic and cholinergic neural pathways mediate stress-induced reactivation of colitis in the rat. Auton Neurosci. 2006; 124:56–68. [PubMed: 16464645]

[38]. Ghia JE, Blennerhassett P, El-Sharkawy RT, Collins SM. The protective effect of the vagus nerve in a murine model of chronic relapsing colitis. Am J Physiol Gastrointest Liver Physiol. 2007; 293:G711–G718. [PubMed: 17673544]

[39]. Liang H, Xu L, Zhou C, Zhang Y, Xu M, Zhang C. Vagal activities are involved in antigen-specific immune inflammation in the intestine. J Gastroenterol Hepatol. 2011; 26:1065–1071. [PubMed: 21371121]

[40]. Ghia JE, Blennerhassett P, Collins SM. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. J Clin Invest. 2008; 118:2209–2218. [PubMed: 18451995]

[41]. Noverr MC, Huffnagle GB. The 'microflora hypothesis' of allergic diseases. Clin Exp Allergy. 2005; 35:1511–1520. [PubMed: 16393316]

[42]. Rodriguez B, Prioult G, Bibiloni R, et al. Germ-free status and altered caecal subdominant microbiota are associated with a high susceptibility to cow's milk allergy in mice. FEMS Microbiol Ecol. 2011; 76:133–144. [PubMed: 21223329]

[43]. Rodriguez B, Prioult G, Hacini-Rachinel F, et al. Infant gut microbiota is protective against cow's milk allergy in mice despite immature ileal T-cell response. FEMS Microbiol Ecol. 2012; 79:192–202. [PubMed: 22029421]

[44]. Bashir ME, Louie S, Shi HN, Nagler-Anderson C. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. J Immunol. 2004; 172:6978–6987. [PubMed: 15153518]

[45]. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host–microbial relationships in the intestine. Science. 2001; 291:881–884. [PubMed: 11157169]

[46]. Noval Rivas M, Burton OT, Wise P, et al. A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. J Allergy Clin Immunol. 2013; 131:201–212. [PubMed: 23201093]

[47]. Tannock GW, Savage DC. Influences of dietary and environmental stress on microbial populations in the murine gastrointestinal tract. Infect Immun. 1974; 9:591–598. [PubMed: 4593471]

[48]. Bailey MT, Lubach GR, Coe CL. Prenatal stress alters bacterial colonization of the gut in infant monkeys. J Pediatr Gastroenterol Nutr. 2004; 38:414–421. [PubMed: 15085020]

[49]. Bailey MT, Coe CL. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Dev Psychobiol. 1999; 35:146–155. [PubMed: 10461128]

[50]. Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterol Motil. 2011; 23:255–e119. [PubMed: 21054680]

[51]. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. J Physiol. 2004; 558:263–275. [PubMed: 15133062]

[52]. Ouwehand AC. Antiallergic effects of probiotics. J Nutr. 2007; 137(suppl 2):794S–797S. [PubMed: 17311977]

[53]. Eutamene H, Lamine F, Chabo C, et al. Synergy between Lactobacillus paracasei and its bacterial products to counteract stress-induced gut permeability and sensitivity increase in rats. J Nutr. 2007; 137:1901–1907. [PubMed: 17634262]

[54]. Gareau MG, Jury J, MacQueen G, Sherman PM, Perdue MH. Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. Gut. 2007; 56:1522–1528. [PubMed: 17339238]

[55]. Anderzen I, Arnetz BB, Soderstrom T, Soderman E. Stress and sensitization in children: a controlled prospective psychophysiological study of children exposed to international relocation. J Psychosom Res. 1997; 43:259–269. [PubMed: 9304552]

[56]. Claes SJ. Corticotropin-releasing hormone (CRH) in psychiatry: from stress to psychopathology. Ann Med. 2004; 36:50–61. [PubMed: 15000347]

[57]. Wallon C, Soderholm JD. Corticotropin-releasing hormone and mast cells in the regulation of mucosal barrier function in the human colon. Ann N Y Acad Sci. 2009; 1165:206–210. [PubMed: 19538308]

[58]. Wallon C, Yang PC, Keita AV, et al. Corticotropin-releasing hormone (CRH) regulates macromolecular permeability via mast cells in normal human colonic biopsies in vitro. Gut. 2008; 57:50–58. [PubMed: 17525093]

[59]. Santos J, Saperas E, Nogueiras C, et al. Release of mast cell mediators into the jejunum by cold pain stress in humans. Gastroenterology. 1998; 114:640–648. [PubMed: 9516384]

[60]. Alonso C, Guilarte M, Vicario M, et al. Maladaptive intestinal epithelial responses to life stress may predispose healthy women to gut mucosal inflammation. Gastroenterology. 2008; 135:163.e1–172.e1. [PubMed: 18455999]

[61]. Hart A, Kamm MA. Review article: mechanisms of initiation and perpetuation of gut inflammation by stress. Aliment Pharmacol Ther. 2002; 16:2017–2028. [PubMed: 12452934]

[62]. Bennett EJ, Tennant CC, Piesse C, Badcock CA, Kellow JE. Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. Gut. 1998; 43:256–261. [PubMed: 10189854]

[63]. Mawdsley JE, Macey MG, Feakins RM, Langmead L, Rampton DS. The effect of acute psychologic stress on systemic and rectal mucosal measures of inflammation in ulcerative colitis. Gastroenterology. 2006; 131:410–419. [PubMed: 16890594]

[64]. Elenkov IJ, Chrousos GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol Metab. 1999; 10:359–368. [PubMed: 10511695]

[65]. Farhadi A, Fields JZ, Keshavarzian A. Mucosal mast cells are pivotal elements in inflammatory bowel disease that connect the dots: stress, intestinal hyperpermeability and inflammation. World J Gastroenterol. 2007; 13:3027–3030. [PubMed: 17589915]

[66]. Pieper S, Brosschot JF, van der Leeden R, Thayer JF. Cardiac effects of momentary assessed worry episodes and stressful events. Psychosom Med. 2007; 69:901–909. [PubMed: 17991822]

[67]. Yin J, Levanon D, Chen JD. Inhibitory effects of stress on postprandial gastric myoelectrical activity and vagal tone in healthy subjects. Neurogastroenterol Motil. 2004; 16:737–744. [PubMed: 15601423]

[68]. O'Connor, DB.; Conner, M. The Handbook of Stress Science: Biology, Psychology, and Health by Contrada RJ & Baum A (Eds.). Springer; New York: 2011. Effects of stress on eating behavior; p. 275-286.

[69]. Kiecolt-Glaser JK. Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge. Psychosom Med. 2010; 72:365–369. [PubMed: 20410248]

[70]. Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? J Allergy Clin Immunol. 2003; 112:420–426. [PubMed: 12897751]

[71]. Benn CS, Thorsen P, Jensen JS, et al. Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. J Allergy Clin Immunol. 2002; 110:72–77. [PubMed: 12110824]

[72]. Penders J, Stobberingh EE, van den Brandt PA, Thijs C. The role of the intestinal microbiota in the development of atopic disorders. Allergy. 2007; 62:1223–1236. [PubMed: 17711557]

[73]. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol. 2012; 129:434–440. 440.e1–2. [PubMed: 22153774]

[74]. Murray CS, Tannock GW, Simon MA, et al. Fecal microbiota in sensitized wheezy and non-sensitized non-wheezy children: a nested case–control study. Clin Exp Allergy. 2005; 35:741–745. [PubMed: 15969664]

[75]. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet. 2003; 361:1869–1871. [PubMed: 12788576]

[76]. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol. 2001; 108:516–520. [PubMed: 11590374]

[77]. Thompson-Chagoyan OC, Fallani M, Maldonado J, et al. Faecal microbiota and short-chain fatty acid levels in faeces from infants with cow's milk protein allergy. Int Arch Allergy Immunol. 2011; 156:325–332. [PubMed: 21720179]

[78]. Gronlund MM, Gueimonde M, Laitinen K, et al. Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the Bifidobacterium microbiota in infants at risk of allergic disease. Clin Exp Allergy. 2007; 37:1764–1772. [PubMed: 17941914]

[79]. McLoughlin RM, Mills KH. Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. J Allergy Clin Immunol. 2011; 127:1097–1107. [PubMed: 21420159]