Stress, Food, and Inflammation: Psychoneuroimmunology and Nutrition at the Cutting Edge

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Abstract: Inflammation is the common link among the leading causes of death. Mechanistic studies have shown how various dietary components can modulate key pathways to inflammation, including sympathetic activity, oxidative stress, transcription factor nuclear factor-κB activation, and proinflammatory cytokine production. Behavioral studies have demonstrated that stressful events and depression can also influence inflammation through these same processes. If the joint contributions of diet and behavior to inflammation were simply additive, they would be important. However, several far more intriguing interactive possibilities are discussed: stress influences food choices; stress can enhance maladaptive metabolic responses to unhealthy meals; and diet can affect mood as well as proinflammatory responses to stressors. Furthermore, because the vagus nerve innervates tissues involved in the digestion, absorption, and metabolism of nutrients, vagal activation can directly and profoundly influence metabolic responses to food, as well as inflammation; in turn, both depression and stress have well-documented negative effects on vagal activation, contributing to the lively interplay between the brain and the gut. As one example, omega-3 fatty acid intake can boost mood and vagal tone, dampen nuclear factor-κB activation and responses to endotoxin, and modulate the magnitude of inflammatory responses to stressors. A better understanding of how stressors, negative emotions, and unhealthy meals work together to enhance inflammation will benefit behavioral and nutritional research, as well as the broader biomedical community.
Key words: interleukin-6; C-reactive protein; proinflammatory cytokines; depression; omega-3; polyunsaturated fatty acid.

CRP = C-reactive protein; **EPA** = eicosapentaenoic acid; **IL** = interleukin; **TNF** = tumor necrosis factor; **LPS** = lipopolysaccharide; ***n*-3** = omega-3; ***n*-6** = omega-6; **NF** = nuclear factor; **PUFA** = polyunsaturated fatty acid.

INTRODUCTION

Together, cardiovascular disease, cancer, and diabetes account for almost 70% of all deaths in the United States; these diseases share inflammation as a common link (1,2). Dietary strategies clearly influence inflammation, as documented through both prospective observational studies as well as randomized, controlled, feeding trials in which participants agree to eat only the food provided to them (1,3). Mechanistic studies have shown how various dietary components can modulate sympathetic activity, oxidative stress, transcription factor nuclear factor (NF)-κB activation, and proinflammatory cytokine production, thus modifying health risks (4).

Behavioral studies have convincingly demonstrated that stress and depression can also influence inflammation through these same pathways. Stressors—and the negative emotions they generate—can enhance sympathetic hyperactivity, promote oxidative stress, augment NF-κB activation, and boost proinflammatory cytokine production (5–7).

If the joint contributions of diet and behavior to inflammation were simply additive, they would certainly be important. However, after briefly reviewing the independent contributions of diet and behavior to inflammation, several far more

intriguing interactive possibilities will be discussed: stress influences food choices; stress enhances maladaptive metabolic responses to unhealthy foods; diet can affect mood as well as proinflammatory responses to stress—and more, as illustrated in Figure 1. The evidence that vulnerabilities are not merely additive provides a window for considering new multidisciplinary prospects.

Diet and Inflammation

Diets that promote inflammation are high in refined starches, sugar, saturated and transfats, and low in omega-3 (*n*-3) fatty acids, natural antioxidants, and fiber from fruits, vegetables, and whole grains (1). For example, women in the Nurses' Health Study who ate a "Westernized" diet (high in red and processed meats, sweets, desserts, French fries, and refined grains) had higher C-reactive protein (CRP), interleukin (IL)-6, E-selectin, soluble vascular adhesion molecule-1, and soluble intercellular adhesion molecule-1 than those with the "prudent" pattern, characterized by higher intakes of fruit, vegetables, legumes, fish, poultry, and whole grains (8).

Further work from the Nurses' Health Study clearly linked transfatty acid consumption with higher inflammation; for example, CRP was 73% higher in women in the highest quintile of consumption compared with those in the lowest quintile, and IL-6 levels were 17% higher in the highest quintile of consumption compared with the lowest quintile (9). The association between transfat consumption and inflammation is a reliable finding across a number of controlled trials and observational studies (3).

The antioxidant properties of vegetables and fruits are thought to be one of the fundamental mechanisms underlying their anti-inflammatory dietary contributions (1). Oxidants, such as superoxide radicals or hydrogen peroxide, that are produced during the metabolism of food can activate the NF-κB pathway, promoting inflammation (4). Higher fruit and vegetable intakes are associated with lower oxidative stress and inflammation (1,4). In fact, some evidence (1,10) suggests that the addition of antioxidants or vegetables may limit or even
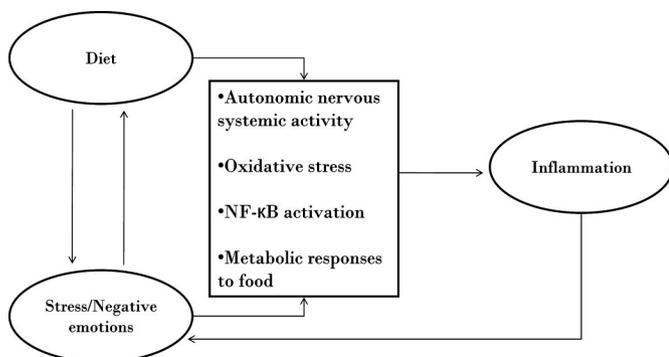
Figure 1. Notable bidirectional relationships among psychological, dietary, and biological pathways to inflammation. *NF* = nuclear factor.

reverse proinflammatory responses to meals high in saturated fat.

Whole grains are healthier than refined grains, because the process of refining carbohydrates results in the elimination of much of the fiber, vitamins, minerals, phytonutrients, and essential fatty acids (1). Furthermore, refined starches and sugars can rapidly alter blood glucose and insulin levels (1), and postprandial hyperglycemia can increase production of free radicals as well as proinflammatory cytokines (11). Medications used to regulate postprandial glucose in diabetics also improve oxidative stress, NF-κB activation, and inflammation, corroborating the relevance of this pathway (12).

Several lines of research (13,14) have implicated inflammation in the pathophysiology of depression. From this perspective, inflammation-enhancing diets could fuel depressive symptoms and could, thus, boost inflammation. One recent article (15) suggested the Mediterranean dietary pattern was potentially protective for the prevention of depressive disorders. Thus, diet influences inflammation; dietary-related inflammation may, in turn, promote depression; and depression can, in turn, advance inflammation.

Depression, Stress, and Inflammation

Psychosocial stress and depression contribute to a greater risk for infection, prolonged infectious episodes, and delayed wound healing—all processes that can fuel proinflammatory cytokine production (16). However, stress and depression can also directly provoke proinflammatory cytokine production in the absence of infection or injury (17,18). Additionally, both clinical depression and subsyndromal depressive symptoms may sensitize or prime the inflammatory response, thus effectively promoting larger cytokine increases in response to stressors as well as antigen challenge (19,20). Furthermore, depression and stress alter inflammation-relevant health behaviors; for example, disturbed sleep, a common response to negative emotions and emotional stress responses, promotes IL-6 production (21). Accordingly, depression and stress can effectively modulate secretion of proinflammatory cytokines both directly and indirectly. Through these pathways, depression and stressful experiences contribute to both acute and chronic proinflammatory cytokine production (22,23).

NF-κB seems to be a prime bridge for stress-induced increases in proinflammatory cytokines and the genes that control their expression (5). For example, NF-κB activity rose 341% within 10 minutes after a laboratory stressor (5). These stress-related changes in NF-κB activity are consistent with other evidence that stress can boost proinflammatory gene expression in peripheral blood mononuclear cells (24,25). Stress-related increases in norepinephrine provoke NF-κB activation, one direct route from the endocrine system to inflammation (5).

Chronic stressors can directly provoke long-term changes in proinflammatory cytokine production, as well as indirectly, by promoting oxidative stress that activates the NF-κB pathway. For example, a 6-year longitudinal study (23) showed that the average annual rate of increase in serum IL-6 was about four times as large in men and women who were chronically stressed by caregiving for a spouse with dementia compared with similar individuals with no caregiving responsibilities. In a sample of mothers who were caregiving for a chronically ill child as well as mothers of healthy children, higher reports of stress were associated with higher oxidative stress activity as measured by levels of F_2-isoprostanes (6). Thus, stress and depression can enhance sympathetic hyperactivity, promote oxidative stress, augment NF-κB activation, and boost proinflammatory cytokine production (5–7). Polyunsaturated fatty acids (PUFAs) also act on these same pathways to influence inflammation.

Dietary Influences on Mood and Proinflammatory Stress Responses: Omega-3 and Omega-6

Arachidonic acid-derived (omega-6 [*n*-6]) eicosanoids (primarily from refined vegetable oils, such as corn, sunflower, and safflower) increase the production of proinflammatory cytokines IL-1, tumor necrosis factor (TNF)-α, and IL-6, operating as precursors of the proinflammatory eicosanoids of the prostaglandin$_2$ series (26,27). In contrast, the *n*-3 PUFAs, found in fish, fish oil, walnuts, wheat germ, and some dietary supplements, such as flax seed products, can curb the production of arachidonic acid-derived eicosanoids (26,27). The *n*-6 and *n*-3 PUFAs compete for the same metabolic pathways; thus, their balance is important (28). Accordingly, it is not surprising that both higher levels of *n*-3 PUFAs as well as lower *n*-6/*n*-3 ratios are associated with lower proinflammatory cytokine production (29).

Based on the links between depression and inflammation (13,14), it is reasonable to expect that dietary *n*-3 and *n*-6 intake could be associated with depression. Epidemiological studies (30) have demonstrated significant inverse relationships between annual fish consumption and major depression—the more fish eaten, the lower the prevalence of serious clinical depression. A number of researchers (31) have shown that depressed patients have, on average, lower plasma levels of *n*-3 than nondepressed individuals; furthermore, they have found evidence that greater severity of depression is linked to lower levels of *n*-3. A number of well-controlled depression treatment studies (31) have found therapeutic benefits post *n*-3

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supplementation, although there are also exceptions. Thus, these dietary pathways have implications for both behavior and inflammation.

Two key n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid, can substantially decrease lipopolysaccharide (LPS)-induced TNF-α expression by blocking NF-κB activation (32,33). Moreover, EPA can also decrease LPS-induced TNF-α messenger ribonucleic acid in vitro, with the modulation of TNF-α expression occurring at the transcriptional level (32). Furthermore, oxidants and oxidized cell components can activate the NF-κB pathway, promoting inflammation (4); the n-3 PUFAs also decrease oxidative stress (34,35). Thus, n-3 PUFA's inhibition of NF-κB transcriptional activity could influence expression of proinflammatory genes.

High-fat meals can stimulate low-grade endotoxemia, i.e., a rise in bacterial endotoxins, inflammatory antigens that are typically found circulating at low concentrations in blood (36). High-fat meals can also induce NF-κB activation in peripheral blood mononuclear cells (37). Importantly, data from endotoxin challenges show that the n-3 PUFAs can diminish these responses, simultaneously modulating changes in the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes.

Bacterial endotoxin (LPS) administration heightens NF-κB activation and produces acute behavioral, neuroendocrine, and inflammatory changes; the characteristic rise in negative mood symptoms after an endotoxin challenge has been used as a behavioral model of depression (38). Fish oil (which contains EPA and docosahexaenoic acid) alters these responses (39,40). For example, rises in plasma adrenocorticotropic hormone, norepinephrine, and TNF-α were, respectively, four-fold, seven-fold, and two-fold lower, after an intravenous fish oil fat emulsion before LPS administration compared with those randomized to no treatment; fish oil also blunted the rise in body temperature compared with controls (40). Subjects who received n-3 supplements for 3 weeks to 4 weeks before an endotoxin challenge had lower norepinephrine, adrenocorticotropic hormone, plasma cortisol, and body temperature responses compared with the same subjects' responses post placebo treatment; differences in TNF-α and IL-6 were not significant in this small sample of 15 subjects (39). Although mood was not assessed in either of these studies, dietary n-3 fatty acids attenuated LPS-induced depression-like behaviors in mice (41).

Paralleling and extending the endotoxin data, other evidence (26) suggested that the n-3 PUFAs may influence immune responses to psychological stressors. For example, medical students who /had lower serum n-3 or higher n-6/n-3 ratios before examinations demonstrated greater TNF-α and interferon-γ production by LPS-stimulated peripheral blood leukocytes during examinations than those with higher n-3 or lower ratios.

Furthermore, another study (28) with older adults suggested that depressive symptoms and n-6/n-3 ratios worked together to enhance inflammation beyond the contribution provided by either variable alone. Although predicted cytokine levels were fairly consistent across n-6/n-3 ratios with low depressive symptoms, higher n-6/n-3 ratios were associated with progressively elevated TNF-α and IL-6 levels as depressive symptoms increased. Accordingly, these studies (26,28) suggested that diet can influence the magnitude of inflammatory responses to stress and depression as well as mood.

Stress Influences Food Choices

Both laboratory and epidemiological studies (42,43) suggested that depression and stressful events motivate less healthy food choices, although there may be greater risk related to being female, overweight, and scoring high on dietary restraint. For example, stress and depression were associated with less fresh fruit consumption as well as greater snack food intake among Chinese college students (44). Female college students (but not males) in Germany, Poland, and Bulgaria who reported more perceived stress ate more sweets and fast foods and fewer fruits and vegetables than those who were less stressed (45). Longitudinal data (46) from the Health Professionals Study showed that men decreased their vegetable intake after divorce or bereavement, and they increased consumption after remarriage. Thus, in general, stress and depression promote less healthy food choices that can boost inflammation. Stress compounds the problem by promoting adverse metabolic responses to unhealthy meals.

Stress Influences Metabolic Responses to Food

Within an hour of eating a meal high in saturated fat, circulating triglycerides rise and can remain elevated for 5 hours to 8 hours (47). Postprandial lipemia (abnormally high lipids after a meal) is associated with Type II diabetes, metabolic syndrome, obesity, and enhanced cardiovascular risk (47). Furthermore, when high-fat meals flood the body with glucose and triglycerides, they provoke spikes in IL-6 and CRP, at the same time enhancing oxidative stress and sympathetic hyperactivity; termed postprandial dysmetabolism, this cascade promotes endothelial dysfunction and, thus, atherogenesis (48). Postprandial lipemia can represent either higher postmeal peaks or delays in clearance, either of which can promote the accumulation of atherogenic-triglyceride-rich remnant lipoproteins (49). Importantly, stress both enhances post-meal peaks and delays clearance.

For example, one study showed that hourly mental stress substantially augmented postprandial lipemia; the total triglycerol and very low-density-lipoprotein-triglycerol areas under the curve were $\geq$50% higher during stress than under control conditions (50). In an elegant study from Stoney and colleagues (51), acute stress also slowed triglyceride clearance after an intravenously administered fat emulsion. Compared with the nonstress session, clearance of an exogenous fat load took 14% longer on average after a laboratory stressor.

Stress alters gastroduodenal motility, slows gastric emptying, and perturbs intestinal transit and colonic motility (52).

Because the vagus nerve innervates tissues involved in the digestion, absorption, and metabolism of nutrients, including the stomach, pancreas, and liver, vagal activation directly and profoundly influences metabolic responses to food (53). For example, vagal activation is important in the regulation of early and peak insulin responses that help to govern postprandial glucose levels (53); in turn, the glucose response to meals helps to determine postprandial inflammation (48). Both depression and stress have well-documented negative effects on vagal activation as indexed by heart rate variability (52,54), providing another pathway through which negative emotions may influence postprandial inflammation. In short, the brain and the gut have a vigorous, ongoing dialogue.

Multidisciplinary Opportunities

Behavioral data are a relative rarity in the nutritional literature, paralleling the infrequent use of dietary measures in behavioral studies; cross talk would benefit both sides. For example, chronic inflammation is one of the primary metabolic changes linked to excessive caloric intake and adiposity, and caloric restriction (consuming ~20% to 30% fewer calories at the same time maximizing micronutrient-dense foods and minimizing energy-dense foods) can have powerful anti-inflammatory effects over periods of months to years (55). However, short-term alterations in meal frequency or timing can also alter inflammation. For example, observant Muslims do not eat or drink during daylight hours during Ramadan, effectively producing a month of prolonged intermittent fasting (56). Comparisons of IL-6 and CRP 1 week before Ramadan, during the last week of Ramadan, and 20 days after Ramadan showed that fasting during the day decreased IL-6 and CRP levels by about 50% compared with pre-Ramadan values, a dramatic reduction in the absence of weight change; a nonfasting group assessed at the same times showed no IL-6 or CRP changes (56).

These provocative data suggest that prolonged intermittent fasting substantially decreases inflammation. Are there concomitant changes in mood? Does prolonged intermittent fasting induce changes in hypothalamic-pituitary-adrenal or sympathetic-adrenal-medullary responses? And, conversely, does mood influence the degree of change?

Fasting also influences the impact of chemotherapy. For example, several strains of mice injected with an aggressive neuroblastoma cell line were starved for 48 hours to 60 hours before receiving extremely high-dose chemotherapy (57). Among mice that ate normally, >40% died from the chemotherapy; in contrast, all of the fasting mice survived, and none showed any visible signs of toxicity. Chemotherapy damages deoxyribonucleic acid in dividing cells, particularly blood cells; in normal cells, fasting slows the cell cycle and, thus, is protective. However, tumor cells do not respond to starvation by slowing cell division, and their continued high replicative rate makes them more vulnerable to chemotherapy (57). In the clinical trials now underway in humans (58), it would be interesting to learn how fasting affects inflammatory responses to chemotherapy and the concomitant increases in depressive symptoms and fatigue, as well as whether fasting alters chemotherapy-induced cognitive changes (59).

A broader and deeper interface between the behavioral and nutritional camps is essential to building our knowledge within each of the separate worlds. Stronger bridges between the fields will also shed light on the forces promoting obesity-related diseases. At a minimum, assessing diet more rigorously in behavioral studies and assessing behavior more routinely in dietary studies would provide important information on what might otherwise be seen as error variance. In short, a better understanding of how stressors, negative emotions, and unhealthy meals work together to enhance inflammation will benefit behavioral and nutritional research, as well as the broader biomedical community.

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