Links Between Behavioral Factors and Inflammation

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This review focuses on the biobehavioral factors that show robust associations with markers of inflammation and discusses the following variables: diet, smoking, coffee, alcohol, exercise, and sleep disruption. Each of these variables has been assessed in large-scale epidemiological studies, and many of them have been assessed in clinical and experimental studies as well. Treatment strategies that target biobehavioral factors have the potential to complement and enhance the benefit of anti-inflammatory medicines.

Understanding the causes of variability in patient response to medicines is critical in all aspects of pharmacology, and recent evidence has implicated environmental and related behavioral factors as contributing to this variability.[1] The number of medicines that seek to treat inflammation has grown exponentially as inflammation is being increasingly recognized as a key predictor of the onset and progression of many diseases (e.g., cardiovascular disease and diabetes). Hence, in this review we focus on the biobehavioral factors that are associated with inflammation, recognizing that the full benefit of anti-inflammatory medicine may be achieved only when steps are taken to address behavioral and lifestyle factors that contribute to risk of inflammation.

The field of psychoneuroimmunology is an emerging interdisciplinary science that examines the impact of behavior and psychological states on immunity. In this regard, psychoneuroimmunology has brought to light the biobehavioral mechanisms that contribute to, and partly explain, variation in inflammation. It is hypothesized that knowledge of such mechanisms will help in the development and use of medications designed to affect the inflammatory response. This review focuses on the biobehavioral factors that show robust associations with markers of inflammation and discusses the following variables: diet, smoking, coffee and alcohol consumption, exercise, and sleep disruption.

DIET

Diet is an important aspect of health behavior and has implications for inflammatory markers. Studies have generally suggested that diets high in fats are associated with increases in markers of inflammation. Later in this article, we review research indicating that diet should be taken into account during analysis of inflammatory markers, with consideration being given to both dietary content and changes in body weight.

Studies have compared dietary patterns characterized as "prudent" (e.g., higher intake of fruit, vegetables, legumes, fish, poultry, and whole grains) with those characterized as "Western" (e.g., higher intake of red and processed meats, sweets, desserts, fried foods, and refined grains) with respect to their association with various markers of inflammation. The prudent dietary pattern was associated with lower plasma concentrations of C-reactive protein (CRP) and also of E-selectin, a marker of endothelial activation. Importantly, these relationships remained robust even after adjusting for age, body mass index (BMI), physical activity, smoking status, and alcohol consumption.[2] In contrast, the Western dietary pattern was associated with higher levels of CRP and the endothelial markers of activation, E-selectin, soluble intercellular adhesion molecule-1, and soluble vascular adhesion molecule-1, after adjusting for all confounders.

In another epidemiological study (N = 5,089), four dietary patterns were statistically derived from food questionnaires. As with the findings for the Western diet, the pattern involving higher intake of fats and processed meats was associated with higher levels of CRP, interleukin-6 (IL-6), and homocysteine.[3] In addition, the dietary pattern involving higher intake of beans, tomatoes, and refined grains was associated with higher levels of soluble intercellular adhesion molecule-1. In contrast, the dietary pattern involving higher intake of whole grains and fruit was associated with lower levels of CRP, IL-6, homocysteine, and soluble intercellular adhesion molecule-1, whereas the pattern involving vegetables and fish was also associated with lower levels of IL-6. These results were found after controlling for demographics and lifestyle factors and were not modified by race/ethnicity.

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With regard to specific foods, a cross-sectional study of 730 women from the Nurses' Health Study found that intake of trans fatty acids was positively related to plasma concentration of CRP, soluble tumor necrosis factor receptor-II, soluble intercellular adhesion molecule-1, and soluble vascular adhesion molecule-1 in linear regression models, after controlling for age; BMI; physical activity; smoking status; alcohol consumption; intake of monounsaturated, polyunsaturated, and saturated fatty acids; and postmenopausal hormone therapy.[4] In contrast, a high-fiber diet was associated with lower plasma levels of IL-6 and tumor necrosis factor receptor-II in the Women's Health Initiative Observational Study. However, there was no association with CRP in these postmenopausal women.[5]

Another aspect of diet that might impact inflammation is body weight and/or changes in body weight. For example, experimental weight loss has demonstrated that changes in daily dietary fat consumption modulate inflammatory markers.[6] Twenty-nine overweight women (average BMI: 32.1 kg/m^2) were randomly assigned to either a high-fat, low-carbohydrate diet or a low-fat, high-carbohydrate diet for 4 weeks. CRP increased by 25% in the high-fat, low-carbohydrate group, even though they lost more weight than the low-fat, high-carbohydrate group did. In contrast, CRP was reduced 43% in the low-fat, high-carbohydrate group. In both groups, IL-6 had increased at the end of 4 weeks, despite overall weight loss. Together, these data suggest that dietary patterns that include higher intake of fat are associated with higher levels of markers of inflammation.

SMOKING

Current tobacco smoking can have robust effects on inflammation and lead to increases in levels of proinflammatory markers. For example, the British Regional Heart Study[7] found higher CRP and fibrinogen levels in current smokers as compared with those who had never smoked, even after controlling for other major cardiovascular risk factors. The Uppsala Longitudinal Study of Adult Men found higher IL-6 levels in both current smokers and former smokers, as compared with older nonsmokers.[8] However, when men who took daily low-dose aspirin treatment were excluded, the relationship was diminished, demonstrating the importance of both behavioral and pharmacological factors.

In addition to the positive associations between current smoking and both IL-6 and CRP, there is a dose–response relationship between the number of past years of smoking and circulating levels of proinflammatory markers.[9] In a study carried out among former cigarette smokers whose use was categorized as either light (<20 cigarettes per day) or heavy (≥20 cigarettes per day), CRP was lower in former light smokers, even after controlling for years elapsed since quitting and for confounders.[7] In fact, although light and heavy current smokers did not show differences in levels of CRP, former light smokers showed a reduction in CRP within 5 years (whereas former heavy smokers required a longer time to do so).

COFFEE

Caffeine is consumed primarily through drinking coffee, but it is important to note that coffee contains a multitude of substances. Hence, studying the effect of coffee on inflammatory markers in humans is complex, further confounded by the fact that different methods of coffee preparation yield varying amounts of caffeine. Filtered coffee must be distinguished from nonfiltered (boiled, French press, or espresso) coffee because the oils of coffee beans are hypercholesterolemic in humans.[10]

In epidemiological studies, nonfiltered coffee consumed at moderate to high doses has been found to be related to increases in CRP, tumor necrosis factor-α, IL-6,[11] and homocysteine.[12] In contrast, the drinking of filtered coffee appears to have minimal impact on markers of inflammation. In fact, in the Iowa Women's Health Study, consumption of coffee was associated with reduced risk of death attributable to inflammatory and cardiovascular diseases.[13] Furthermore, among women with type 2 diabetes, higher consumption of caffeinated coffee was significantly associated with lower plasma concentrations of E-selectin and CRP, further suggesting that the consumption of filtered coffee is inversely associated with markers of inflammation.[14]

To address the limitations of epidemiological studies and correlative observations, one experimental study employed a randomized controlled design to compare the effects of caffeine capsules, filtered coffee, and placebo on markers of inflammation. Verhoef and colleagues[15] concluded that, although pure caffeine led to increases in homocysteine, caffeine alone had only 25–50% of the homocysteine-raising effect of paper-filtered coffee, despite having a similar amount of caffeine. This suggests that compounds other than caffeine that are present in coffee can raise homocysteine levels.

ALCOHOL

The association between alcohol consumption and markers of inflammation (e.g., IL-6 and CRP) is widely reproducible across studies, indicating that increases in the amount of alcohol intake (not the type of alcoholic beverage consumed) are associated with increases in IL-6 and CRP. However, the association between alcohol consumption and proinflammatory cytokines typically follows a U- or J-shaped pattern, in which circulating levels of CRP are lower in moderate drinkers as compared with nondrinkers, whereas heavy drinkers showed the highest levels of inflammation (see Health Professionals Follow-up Study and Nurses' Health Study II[16]). Similar findings are found for circulating levels of IL-6,[16,17] although the effects are more robust in men.[18]

The threshold at which alcohol consumption leads to increases in CRP and IL-6 is not well defined, partly because of differences in the way alcohol intake is reported. However, an alcohol-intake-controlled trial has found that drinking 30 g of alcohol per day (i.e., two drinks) for 12 weeks resulted in lower levels of CRP as compared with abstinence from alcohol,[19] with similar CRP-lowering results for those who drank 30–40 g of alcohol per day for 3 weeks.[20] Together, these data suggest that alcohol consumption will lead to increases in markers of inflammation only when consumption exceeds the threshold level of 30 g per day.

EXERCISE

Regular physical activity is thought to be associated with lower levels of circulating inflammatory markers (for a review, see

ref. 21). In two major cross-sectional epidemiological studies (the National Health and Nutrition Examination Survey (NHANES) and Pravastatin Inflammation/CRP Evaluation (PRINCE)), CRP was found to be substantially lower among those who reported engaging in physical activity, even after controlling for a wide range of confounding variables. Likewise, randomized exercise intervention studies have also demonstrated that increases in daily physical activity lead to reductions in levels of CRP and IL-6 in healthy populations as well as in patients.[22–24] Whether these reductions in CRP and IL-6 remain valid after controlling for BMI is still under debate.[25] However, studies that have focused on metabolic syndrome have revealed more consistent associations between cardiorespiratory fitness and lower circulating levels of inflammation, even after controlling for BMI.[26]

Research in the past 10 years has advanced our understanding of how physical activity and associated contraction of skeletal muscle may affect overall inflammatory markers.[27] Whereas acute as well as prolonged exercise increase the level of circulating IL-6, such increases in IL-6 (when they occur repeatedly) induce increases in anti-inflammatory cytokines.[28] In turn, these anti-inflammatory cytokines (e.g., IL-1 receptor antagonist, IL-10) suppress other proinflammatory cytokines, such as tumor necrosis factor-α, which ultimately contributes to lower levels of markers of systemic inflammation in association with higher levels of physical activity.

SLEEP DISRUPTION

Shorter sleep duration and chronic insomnia, as well as acute (i.e., one-night) sleep loss, are associated with increases in CRP, IL-6, and other inflammatory markers. Several studies that have experimentally examined the impact of sleep disruption on cytokine levels found that one night of total sleep deprivation or more modest (only part of the night) sleep loss can lead to increases in daytime levels of IL-6, CRP, and soluble tumor necrosis factor receptor due to increases in activation of inflammatory signaling pathways.[29,30]

Consistent with these experimental data, observational studies have shown that shift workers[31] have increases in circulating levels of inflammatory markers, as do older adults, who have poorer sleep than younger adults.[32] Moreover, epidemiological data suggest that, in men, self-reported poor sleep quality is associated with elevations in CRP, after controlling for potential confounding variables.[33]

CONCLUSION

We have very little data on the contribution of behavioral factors to medication effects on inflammation because most (if not all) pharmacology studies look only at drug action, without taking into account biobehavioral variability among individuals to understand differential response rates and/or risk profiles for drug benefit. This review has highlighted the results of psychoneuroimmunology studies that examined the effects of behavioral factors on inflammation and found substantial evidence for the influence of such factors on markers of inflammation. Future studies that focus on the action of pharmacological agents on inflammatory responses should yield information about biobehavioral factors as well, so as to determine whether interindividual differences in responses to these medicines are related in part to such factors.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

1. Wilkinson, G.R. Drug metabolism and variability among patients in drug response. *N. Engl. J. Med.* **352**, 2211–2221 (2005).
2. Lopez-Garcia, E. *et al*. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *Am. J. Clin. Nutr.* **80**, 1029–1035 (2004).
3. Nettleton, J.A. *et al*. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am. J. Clin. Nutr.* **83**, 1369–1379 (2006).
4. Lopez-Garcia, E. *et al*. Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. *J. Nutr.* **135**, 562–566 (2005).
5. Ma, Y. *et al*. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. *Nutrition* **24**, 941–949 (2008).
6. Rankin, J.W. & Turpyn, A.D. Low carbohydrate, high fat diet increases C-reactive protein during weight loss. *J. Am. Coll. Nutr.* **26**, 163–169 (2007).
7. Wannamethee, S.G., Lowe, G.D., Shaper, A.G., Rumley, A., Lennon, L. & Whincup, P.H. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur. Heart J.* **26**, 1765–1773 (2005).
8. Helmersson, J., Larsson, A., Vessby, B. & Basu, S. Active smoking and a history of smoking are associated with enhanced prostaglandin F(2alpha), interleukin-6 and F2-isoprostane formation in elderly men. *Atherosclerosis* **181**, 201–207 (2005).
9. Mendall, M.A. *et al*. C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. *Eur. Heart J.* **21**, 1584–1590 (2000).
10. Ranheim, T. & Halvorsen, B. Coffee consumption and human health—beneficial or detrimental?—Mechanisms for effects of coffee consumption on different risk factors for cardiovascular disease and type 2 diabetes mellitus. *Mol. Nutr. Food Res.* **49**, 274–284 (2005).
11. Zampelas, A., Panagiotakos, D.B., Pitsavos, C., Chrysohoou, C. & Stefanadis, C. Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. *Am. J. Clin. Nutr.* **80**, 862–867 (2004).
12. Chrysohoou, C. *et al*. The associations between smoking, physical activity, dietary habits and plasma homocysteine levels in cardiovascular disease-free people: the 'ATTICA' study. *Vasc. Med.* **9**, 117–123 (2004).
13. Andersen, L.F., Jacobs, D.R. Jr., Carlsen, M.H. & Blomhoff, R. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. *Am. J. Clin. Nutr.* **83**, 1039–1046 (2006).
14. Lopez-Garcia, E., van Dam, R.M., Qi, L. & Hu, F.B. Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. *Am. J. Clin. Nutr.* **84**, 888–893 (2006).
15. Verhoef, P., Pasman, W.J., Van Vliet, T., Urgert, R. & Katan, M.B. Contribution of caffeine to the homocysteine-raising effect of coffee: a randomized controlled trial in humans. *Am. J. Clin. Nutr.* **76**, 1244–1248 (2002).
16. Pai, J.K., Hankinson, S.E., Thadhani, R., Rifai, N., Pischon, T. & Rimm, E.B. Moderate alcohol consumption and lower levels of inflammatory markers in US men and women. *Atherosclerosis* **186**, 113 (2006).
17. Volpato, S. *et al*. Relationship of alcohol intake with inflammatory markers and plasminogen activator inhibitor-1 in well-functioning older adults: the Health, Aging, and Body Composition study. *Circulation* **109**, 607–612 (2004).
18. Welsh, P., Woodward, M., Rumley, A. & Lowe, G. Associations of plasma pro-inflammatory cytokines, fibrinogen, viscosity and C-reactive protein

with cardiovascular risk factors and social deprivation: the fourth Glasgow MONICA study. *Br. J. Haematol.* **141**, 852–861 (2008).
19. Estruch, R. *et al*. Different effects of red wine and gin consumption on inflammatory biomarkers of atherosclerosis: a prospective randomized crossover trial. Effects of wine on inflammatory markers. *Atherosclerosis* **175**, 117–123 (2004).
20. Sierksma, A., van der Gaag, M.S., Kluft, C. & Hendriks, H.F. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels; a randomized, diet-controlled intervention study. *Eur. J. Clin. Nutr.* **56**, 1130–1136 (2002).
21. Kasapis, C. & Thompson, P.D. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J. Am. Coll. Cardiol.* **45**, 1563–1569 (2005).
22. Esposito, K. *et al*. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* **289**, 1799–1804 (2003).
23. Kohut, M.L. *et al*. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav. Immun.* **20**, 201–209 (2006).
24. Nicklas, B.J. *et al*. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *Am. J. Clin. Nutr.* **79**, 544–551 (2004).
25. Hamer, M. The relative influences of fitness and fatness on inflammatory factors. *Prev. Med.* **44**, 3–11 (2007).
26. Aronson, D. *et al*. The association between cardiorespiratory fitness and C-reactive protein in subjects with the metabolic syndrome. *J. Am. Coll. Cardiol.* **44**, 2003–2007 (2004).
27. Pedersen, B.K. & Febbraio, M. Muscle-derived interleukin-6—a possible link between skeletal muscle, adipose tissue, liver, and brain. *Brain Behav. Immun.* **19**, 371–376 (2005).
28. Petersen, A.M. & Pedersen, B.K. The anti-inflammatory effect of exercise. *J. Appl. Physiol.* **98**, 1154–1162 (2005).
29. Irwin, M.R., Wang, M., Campomayor, C.O., Collado-Hidalgo, A. & Cole, S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch. Intern. Med.* **166**, 1756–1762 (2006).
30. Irwin, M.R., Olmstead, R., Valladares, E.M., Breen, E.C. & Ehlers, C.L. Tumor necrosis factor antagonism normalizes rapid eye movement sleep in alcohol dependence. *Biol. Psychiatry* **66**, 191–195 (2009).
31. Zheng, H., Patel, M., Hryniewicz, K. & Katz, S.D. Association of extended work shifts, vascular function, and inflammatory markers in internal medicine residents: a randomized crossover trial. *JAMA* **296**, 1049–1050 (2006).
32. Vgontzas, A.N. *et al*. Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications. *J. Clin. Endocrinol. Metab.* **88**, 2087–2095 (2003).
33. Liukkonen, T. *et al*. C-reactive protein levels and sleep disturbances: observations based on the Northern Finland 1966 Birth Cohort study. *Psychosom. Med.* **69**, 756–761 (2007).