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Links between behavioral factors and inflammation

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Abstract

This review focuses on those biobehavioral factors that show robust associations with markers of inflammation, including discussion of 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 in clinical and experimental studies as well. Treatment strategies that target biobehavioral factors have the potential to complement and add to the benefit of anti-inflammatory medicines.

Introduction

Understanding the causes of variability in responses to medicines is critical in all aspects of pharmacology, and recent evidence has implicated environmental and related behavioral factors as contributing to variability in patient's drug responses (1). Medicines that impact inflammation have grown exponentially, as inflammation is increasingly recognized as a key predictor of the onset and progression of many diseases (e.g., cardiovascular disease, diabetes, etc). 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 only be fully achieved when steps are taken to address behavioral and lifestyle factors that contribute to inflammatory risk.

The field of psychoneuroimmunology (PNI) is an emerging interdisciplinary science that examines the impact of behavior and psychological states on immunity. In this regard, PNI 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 impact the inflammatory response. This review will focus on those biobehavioral factors that show robust associations with markers of inflammation including discussion of the following variables: diet, smoking, coffee, alcohol, exercise and sleep disruption.

Diet

Diet is an important aspect of health behavior that has implications for inflammatory markers, with findings generally suggesting that diets high in fats are associated with increases in markers of inflammation. Below, research is reviewed to indicate that diet should be taken into account during analysis of inflammatory markers, with both consideration of dietary content, as well as changes in body weight.

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Studies have compared the association between dietary patterns that are characterized as "prudent" (e.g., higher intake of fruit, vegetables, legumes, fish, poultry, and whole grains) versus those that are characterized as "Western" (e.g., higher intake of red and processed meats, sweets, desserts, French fries, and refined grains). The prudent dietary pattern was associated with lower levels of plasma concentrations of C-reactive protein (CRP) and E-selectin, a marker of endothelial activation. Importantly, these relationships remained robust even after adjustment 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 (sICAM-1) and soluble vascular adhesion molecule (sVCAM-1) after adjustment for all confounders.

In another epidemiological study (N= 5089), four dietary patterns were statistically derived from food questionnaires. As with the findings for the Western diet, higher intake of the fats and processed meats pattern was associated with higher levels of CRP, interleukin-6 (IL-6), and homocysteine (3). In addition, higher intake of the beans, tomatoes, and refined grains pattern was associated with higher levels of sICAM-1. In contrast, higher intake of the whole grains and fruit pattern was associated with lower levels of CRP, IL-6, homocysteine and sICAM-1, and the vegetables and fish pattern 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.

With regard to specific foods, a cross-sectional study of 730 women from the Nurses' Health Study found that trans fatty acid intake was positively related to plasma concentration of CRP, soluble tumor necrosis factor receptor II (sTNFR-II), sICAM-1, and sVCAM-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 TNF-RII 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 modulates inflammatory markers (6). Twenty-nine overweight women (average BMI: 32.1 kg/m^2) were randomly assigned to a high fat, low carbohydrate diet, or a low fat, high carbohydrate diet for four weeks. CRP increased 25% in the high fat, low carbohydrate group, even though they lost more weight than the low fat, high carbohydrate group. In contrast, CRP was reduced 43% in the low fat, high carbohydrate group. For both groups, IL-6 increased at the end of four 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 pro-inflammatory markers. For example, the British Regional Heart Study (7) found higher CRP and fibrinogen levels in current smokers as compared to those who had never smoked, even after controlling for other major cardiovascular risk factors. The Uppsala Longitudinal Study of Adult Men (ULSAM) found higher IL-6 levels in both current smokers and former smokers, as compared to older non-smokers (8). However, when men who took daily low-dose aspirin treatment were excluded, the relationship was diminished, demonstrating the importance of both behavioral and pharmacologic factors.

In addition to the positive association between current smoking and IL-6 and CRP, there is a dose-response relationship between the number of *past* years of smoking and circulating levels of pro-inflammatory markers (9). Among ex-cigarette smokers who were divided into those who had been light and heavy smokers (<20 and >20 cigarettes per day, respectively), CRP was lower in ex-light smokers, even when controlling for years since quitting and for confounders (7). In fact, although light and heavy current smokers did not show different levels of CRP, light ex-smokers showed a reduction in CRP within 5 years (while ex-heavy smokers required longer).

Coffee

Caffeine is primarily obtained 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 human studies is complex, and further confounded by the fact that different methods of coffee preparation yield varying amounts of caffeine. Filtered coffee must be distinguished from non-filtered (boiled, French press or espresso) coffee since the oils of coffee beans are hypercholesterolemic in humans (10).

In epidemiologic studies, non-filtered coffee consumed at moderate to high doses has been found to be related to increases in CRP, TNF-a and IL-6 (11) and homocysteine (12). In contrast, filtered coffee drinking appears to have minimal impact on markers of inflammation. In fact, consumption of coffee was associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study (13). Furthermore, among women with type 2 diabetes, higher caffeinated coffee consumption was significantly associated with lower plasma concentrations of E-selectin and C-reactive protein, further suggesting that filtered coffee consumption 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 and compared 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 in coffee can raise homocysteine levels.

Alcohol

The association of 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, is associated with increases of IL-6 and CRP. However, the association between alcohol consumption and pro-inflammatory cytokines typically follows a U- or J-shaped pattern, in which circulating levels of CRP are lower in moderate drinkers as compared to non-drinkers whereas heavy drinkers showed the highest levels of inflammation (see Health Professionals Follow-up Study and Nurse's Health Study II (NHSII) (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 due to differences in the way alcohol intake is reported. However, an alcohol-intake-controlled trial has found that drinking 30g of alcohol per day (i.e., two drinks) for 12-weeks resulted in lower levels of CRP as compared to abstinence (19), with similar CRP-lowering results for those that drank 30–40g of alcohol per day for 3-weeks (20). Together,

these data suggest that alcohol consumption that exceeds at least 30 g of alcohol per day is needed to lead to increases in markers of inflammation.

Exercise

Regular physical activity is thought to be associated with lower levels of circulating inflammatory markers (for a review, see 21). In two major cross-sectional epidemiological studies (NHANES and PRINCE), CRP was found to be substantially lower among those who reported amounts of 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 leads to reductions in levels of CRP and IL-6 in healthy as well as patient populations (22–24). Whether this reduction of CRP and IL-6 remains true 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 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 impact overall inflammatory markers (27). Whereas acute as well as prolonged exercise increases the level of circulating IL-6, such increases of IL-6 (when occurring repeatedly) induce increases in anti-inflammatory cytokines (28). In turn, these anti-inflammatory cytokines (e.g., IL-1ra, IL-10) suppress other pro-inflammatory cytokines, such as TNF-alpha, which ultimately contributes to lower levels of markers of systemic inflammation in association with higher amounts of physical activity.

Sleep disruption

Shorter sleep duration and chronic insomnia, as well as acute (i.e., one night) sleep loss, is associated with increases in CRP, IL-6 and other inflammatory markers. Several studies have experimentally examined the impact of sleep disruption and cytokine levels, and found one night total sleep deprivation as well as more modest sleep loss for only part of the night leads to increases in daytime levels of IL-6, CRP and sTNF-R, due to increases in activation of inflammatory signaling pathways (29,30).

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

Conclusion

We have very little data about how behavioral factors impact medication effects of inflammation, because most (if not all) pharmacology studies simply look at drug action without taking into account biobehavioral variability to understand differential response rates and / or risk profiles for drug benefit. This review has highlighted the results of PNI studies examining the effect of behavioral factors on inflammation, and finds 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 acquire information about these factors to understand whether differences in response to such medicines is related in part to biobehavioral factors.

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