CANNABIDIOL AND INFLAMMATION

Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress.

http://www.ncbi.nlm.nih.gov/pubmed/21238581

Oxidative stress with reactive oxygen species generation is a key weapon in the arsenal of the immune system for fighting invading pathogens and initiating tissue repair. If excessive or unresolved, however, immune-related oxidative stress can initiate further increasing levels of oxidative stress that cause organ damage and dysfunction. Targeting oxidative stress in various diseases therapeutically has proven more problematic than first anticipated given the complexities and perversity of both the underlying disease and the immune response. However, growing evidence suggests that the endocannabinoid system, which includes the CB_1 and CB_2 G-protein-coupled receptors and their endogenous lipid ligands, may be an area that is ripe for therapeutic exploitation. In this context, the related nonpsychotropic cannabinoid cannabidiol, which may interact with the endocannabinoid system but has actions that are distinct, offers promise as a prototype for anti-inflammatory drug development. This review discusses recent studies suggesting that cannabidiol may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain.

Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors.

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Certain types of nonpsychoactive cannabinoids can potentiate glycine receptors (GlyRs), an important target for nociceptive regulation at the spinal level. However, little is known about the potential and mechanism of glycinergic cannabinoids for chronic pain treatment. We report that systemic and intrathecal administration of cannabidiol (CBD), a major nonpsychoactive component of marijuana, and its modified derivatives significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in rodents. The cannabinoids significantly potentiate glycine currents in dorsal horn neurons in rat spinal cord slices. The analgesic potency of 11 structurally similar cannabinoids is positively correlated with cannabinoid potentiation of the α3 GlyRs. In contrast, the cannabinoid analgesia is neither correlated with their binding affinity for CB1 and CB2 receptors nor with their psychoactive side effects. NMR analysis reveals a direct interaction between CBD and S296 in the third transmembrane domain of purified α3 GlyR. The cannabinoid-induced analgesic effect is absent in mice lacking the α3 GlyRs. Our findings suggest that the α3 GlyRs mediate glycinergic cannabinoid-induced suppression of chronic pain. These cannabinoids may represent a novel class of therapeutic agents for the treatment of chronic pain and other diseases involving GlyR dysfunction.

Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors.

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Inflammation in the central nervous system (CNS) is a complex process that involves a multitude of molecules and effectors, and it requires the transmigration of blood leukocytes across the blood-brain barrier (BBB) and the activation of resident immune cells. Cannabidiol (CBD), a non-psychotropic cannabinoid constituent of Cannabis sativa, has potent anti-inflammatory and immunosuppressive properties. Yet, how this compound modifies the deleterious effects of inflammation in TMEV-induced demyelinating disease (TMEV-IDD) remains unknown. Using this viral model of multiple sclerosis (MS), we demonstrate that CBD decreases the transmigration of blood leukocytes by downregulating the expression of vascular cell adhesion molecule-1 (VCAM-1), chemokines (CCL2 and CCL5) and the proinflammatory cytokine IL-1β, as well as by attenuating the activation of microglia. Moreover, CBD administration at the time of viral infection exerts long-lasting effects, ameliorating motor deficits in the chronic phase of the disease in conjunction with reduced microglial activation and pro-inflammatory cytokine production. Adenosine A2A receptors participate in some of the anti-inflammatory effects of CBD, as the A2A antagonist ZM241385 partially blocks the protective effects of CBD in the initial stages ofinflammation. Together, our findings highlight the anti-inflammatory effects of CBD in this viral model of MS and demonstrate the significant therapeutic potential of this compound for the treatment of pathologies with an inflammatory component.

Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement.

http://www.ncbi.nlm.nih.gov/pubmed/22163051

Peroxisome proliferator-activated receptor-γ (PPARγ) has been reported to be involved in the etiology of pathological features of Alzheimer's disease (AD). Cannabidiol (CBD), a Cannabis derivative devoid of psychomimetic effects, has attracted much attention because of its promising neuroprotective properties in rat AD models, even though the mechanism responsible for such actions remains unknown. This study was aimed at exploring whether CBD effects could be subordinate to its activity at PPARγ, which has been recently indicated as its putative binding site. CBD actions on β-amyloid-induced neurotoxicity in rat AD models, either in presence or absence of PPAR antagonists were investigated. Results showed that the blockade of PPARγ was able to significantly blunt CBD effects on reactive gliosis and subsequently on neuronal damage. Moreover, due to its interaction at PPARγ, CBD was observed to stimulate hippocampal neurogenesis. All these findings report the inescapable role of this receptor in mediating CBD actions, here reported.

Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis.

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Enteric glial cells (EGC) actively mediate acute and chronic inflammation in the gut; EGC proliferate and release neurotrophins, growth factors, and pro-inflammatory cytokines which, in turn, may amplify the immune response, representing a very important link between the nervous and immune systems in the intestine. Cannabidiol (CBD) is an interesting compound because of its ability to control reactive gliosis in the CNS, without any unwanted psychotropic effects. Therefore the rationale of our study was to investigate the effect of CBD on intestinal biopsies from patients with ulcerative colitis (UC) and from intestinal segments of mice with LPS-induced intestinal inflammation. CBD markedly counteracted reactive enteric gliosis in LPS-mice trough the massive reduction of astroglial signalling neurotrophin S100B. Histological, biochemical and immunohistochemical data demonstrated that S100B decrease was associated with a considerable decrease in mast cell and macrophages in the intestine of LPS-treated mice after CBD treatment. Moreover the treatment of LPS-mice with CBD reduced TNF-α expression and the presence of cleaved caspase-3. Similar results were obtained in ex vivo cultured human derived colonic biopsies. In biopsies of UC patients, both during active inflammation and in remission stimulated

with LPS+INF-γ, an increased glial cell activation and intestinal damage were evidenced. CBD reduced the expression of S100B and iNOS proteins in the human biopsies confirming its well documented effect in septic mice. The activity of CBD is, at least partly, mediated via the selective PPAR-gamma receptor pathway. CBD targets enteric reactive gliosis, counteracts the inflammatory environment induced by LPS in mice and in human colonic cultures derived from UC patients. These actions lead to a reduction of intestinal damage mediated by PPARgamma receptor pathway. Our results therefore indicate that CBD indeed unravels a new therapeutic strategy to treat inflammatory bowel diseases.

Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy.

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Diabetic cardiomyopathy was characterized by declined diastolic and systolic myocardial performance associated with increased oxidative-nitrative stress, nuclear factor-κB and mitogen-activated protein kinase (c-Jun N-terminal kinase, p-38, p38α) activation, enhanced expression of adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1), tumor necrosis factor-α, markers of fibrosis (transforming growth factor-β, connective tissue growth factor, fibronectin, collagen-1, matrix metalloproteinase-2 and -9), enhanced cell death (caspase 3/7 and poly[adenosine diphosphate-ribose] polymerase activity, chromatin fragmentation, and terminal deoxynucleotidyl transferase dUTP nick end labeling), and diminished Akt phosphorylation. Remarkably, CBD attenuated myocardial dysfunction, cardiac fibrosis, oxidative/nitrative stress, inflammation, cell death, and interrelated signaling pathways. Furthermore, CBD also attenuated the high glucose-induced increased reactive oxygen species generation, nuclear factor-κB activation, and cell death in primary human cardiomyocytes. Collectively, these results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications, and perhaps other cardiovascular disorders, by attenuating oxidative/nitrative stress, inflammation, cell death and fibrosis.

Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption.

http://www.ncbi.nlm.nih.gov/pubmed/17384130

A nonpsychoactive cannabinoid cannabidiol (CBD) has been shown to exert potent anti-inflammatory and antioxidant effects and has recently been reported to lower the incidence of diabetes in nonobese diabetic mice and to preserve the blood-retinal barrier in experimental diabetes. In this study we have investigated the effects of CBD on high glucose (HG)-induced, mitochondrial superoxide generation, NF-kappaB activation, nitrotyrosine formation, inducible nitric oxide synthase (iNOS) and adhesion molecules ICAM-1 and VCAM-1 expression, monocyte-endothelial adhesion, transendothelial migration of monocytes, and disruption of endothelial barrier function in human coronary artery endothelial cells (HCAECs). HG markedly increased mitochondrial superoxide generation (measured by flow cytometry using MitoSOX), NF-kappaB activation, nitrotyrosine formation, upregulation of iNOS and adhesion molecules ICAM-1 and VCAM-1, transendothelial migration of monocytes, and monocyte-endothelial adhesion in HCAECs. HG also decreased endothelial barrier function measured by increased permeability and diminished expression of vascular endothelial cadherin in HCAECs. Remarkably, all the above mentioned effects of HG were attenuated by CBD pretreatment. Since a disruption of the endothelial function and integrity by HG is a crucial early event underlying the development of various diabetic complications, our results suggest that CBD, which has recently been approved for the treatment of inflammation, pain, and spasticity associated with multiple sclerosis in humans, may have significant therapeutic benefits against diabetic complications and atherosclerosis.

The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in chronic inflammatory and neuropathic pain.

http://www.ncbi.nlm.nih.gov/pubmed/17157290

Cannabidiol, the major psycho-inactive component of cannabis, has substantial anti-inflammatory and immunomodulatory effects. This study investigated its therapeutic potential on neuropathic (sciatic nerve chronic constriction) and inflammatory pain (complete Freund's adjuvant intraplantar injection) in rats. In both models, daily oral treatment with cannabidiol (2.5-20 mg/kg to neuropathic and 20 mg/kg to adjuvant-injected rats) from day 7 to day 14 after the injury, or intraplantar injection, reduced hyperalgesia to thermal and mechanical stimuli. In the neuropathic animals, the anti-hyperalgesic effect of cannabidiol (20 mg/kg) was prevented by the vanilloid antagonist capsazepine (10 mg/kg, i.p.), but not by cannabinoid receptor antagonists. Cannabidiol's activity was associated with a reduction in the content of several mediators, such as prostaglandin E(2) (PGE(2)), lipid peroxide and nitric oxide (NO), and in the over-activity of glutathione-related enzymes. Cannabidiol only reduced the over-expression of constitutive endothelial NO synthase (NOS), without significantly affecting the inducible form (iNOS) in inflamed paw tissues. Cannabidiol had no effect on neuronal and iNOS isoforms in injured sciatic nerve. The compound's efficacy on neuropathic pain was not accompanied by any reduction in nuclear factor-kappaB (NF-kappaB) activation and tumor necrosis factor alpha (TNFalpha) content. The results indicate a potential for therapeutic use ofcannabidiol in chronic painful states.

Cannabidiol lowers incidence of diabetes.

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Cannabidinoids are components of the Cannabis sativa (marijuana) plant that have been shown capable of suppressing inflammation and various aspects of cell-mediated immunity. Cannabidiol (CBD), a non-psychoactive cannabidinoid has been previously shown by us to suppress cell-mediated autoimmune joint destruction in an animal model of rheumatoid arthritis. We now report that CBD treatment significantly reduces the incidence of diabetes in NOD mice from an incidence of 86% in non-treated control mice to an incidence of 30% in CBD-treated mice. CBD treatment also resulted in the significant reduction of plasma levels of the pro-inflammatory cytokines, IFN-gamma and TNF-alpha. Th1-associated cytokine production of in vitro activated T-cells and peritoneal macrophages was also significantly reduced in CBD-treated mice, whereas production of the Th2-associated cytokines, IL-4 and IL-10, was increased when compared to untreated control mice. Histological examination of the pancreatic islets of CBD-treated mice revealed significantly reduced insulitis. Our results indicate that CBD can inhibit and delay destructive insulitis and inflammatory Th1-associated cytokine production in NOD mice resulting in a decreased incidence of diabetes possibly through an immunomodulatory mechanism shifting the immune response from Th1 to Th2 dominance.

INFLAMMATION (CHRONIC)

Of the ten leading causes of *mortality* in the United States, ***chronic, low-level inflammation*** contributes to the pathogenesis of at least seven. These include heart disease, cancer, chronic lower respiratory disease, stroke, Alzheimer's disease, diabetes, and nephritis (Centers for Disease Control and Prevention 2011; Bastard et al. 2006; Cao 2011, Jha et al. 2009; Ferrucci et al. 2010; Glorieux et al. 2009; Kundu et al. 2008; Murphy 2012; Singh et al. 2011).

Chronic inflammation can be triggered by cellular stress and dysfunction, such as that caused by excessive calorie consumption, elevated blood sugar levels, and oxidative stress. It is now clear that

the destructive capacity of *chronic* inflammation is unprecedented among physiologic processes (Karin et al. 2006).

The danger of chronic, low-level inflammation is that its ***silent*** nature belies its ***destructive*** power.

In fact, stress-induced inflammation, once triggered, can persist undetected for years, or even decades, propagating cell death throughout the body. Due to the fact that it contributes so greatly to deterioration associated with the aging process, this silent state of chronic inflammation has been coined “inflammaging”.

Chronic low-level inflammation may be **threatening your health** at this very moment, without you realizing it. In this protocol you will learn about low-cost blood tests that can assess the inflammatory state within your body. You’ll also discover novel approaches that combat chronic inflammation to help avoid age-related health decline.

Circulating sugars, primarily *glucose* and *fructose*, are culprits as well. When these “blood sugars” come in contact with proteins and lipids a damaging reaction occurs forming compounds called**advanced glycation end products (AGEs).** AGEs bind to the cell-surface receptor called *receptor for advanced glycation end products*, or RAGE. Upon activation, RAGE triggers the movement of the inflammatory mediator *nuclear factor kappa-B* (NF-kB) to the nucleus, where it activates numerous inflammatory genes (Mosquera 2010). Advanced glycation end products are primarily formed *in vivo,* and glycation is exacerbated by elevated blood sugar levels. However, dietary AGEs also contribute to inflammation; they are abundant in foods cooked at high temperatures, especially red meat (Witko-Sarsat et al. 1998; Vlassara et al. 2002).

Following is a list of some of the most prominent markers of inflammation used in research and diagnosis. Some can be detected by blood tests (see “Diagnosis and Conventional Treatment of Chronic Inflammation”, below):

Tumor necrosis factor alpha (TNF-α) is an intercellular signaling protein called a cytokine, which can be released by multiple types of immune cells in response to cellular damage, stress, or infection. Originally identified as an anti-tumor compound produced by macrophages (immune cells) (Green et al. 1976), TNF-α is required for proper immune surveillance and function. Acting alone or with other inflammatory mediators, TNF-α slows the growth of many pathogens. It activates the bactericidal effects of neutrophils, and is required for the replication of several other immune cell types (Sethi et al. 2008). Excessive TNF-α, however, can lead to a chronic inflammatory state, can increase thrombosis (blood clotting) and decrease cardiac contractility, and may be implicated in tumor initiation and promotion (Kundu et al. 2008).

Nuclear factor kappa-B (NF-kB) is important in the initiation of the inflammatory response. When cells are exposed to damage signals (such as TNF-α or oxidative stress), they activate NF-kB, which turns on the expression of over 400 genes involved in the inflammatory response (Sethi et al. 2008). These include other inflammatory cytokines, and pro-inflammatory enzymes including***cyclooxygenase-2*** (COX-2) and ***lipoxygenase***. COX-2 is the enzyme responsible for synthesizing pro-inflammatory prostaglandins, and is the target of non-steroidal anti-inflammatory drugs (ibuprofen, aspirin) and COX-2 inhibitors (Celebrex®).

Interleukins are cytokines that have many functions in the promotion and resolution of inflammation. Pro-inflammatory interleukins that have been the subject of most research include IL-1β, IL-6, and IL-8. IL-1β helps immune cells to move out of blood vessels and into damaged or dysfunctional tissues. IL-6 has both pro-inflammatory and anti-inflammatory roles, and coordinates the production of compounds required during the progression and resolution of acute inflammation. IL-8 is expressed by both immune and non-immune cells, and helps to attract neutrophils (immune cells that can destroy pathogens) to sites of injury.

C-reactive protein (CRP) is an acute-phase protein, one of several proteins rapidly produced by the liver during an inflammatory response. Its primary goal in acute inflammation is to coat damaged

cells to make them easier to recognize by other immune cells (Meyer 2010). CRP elevation above basal levels is not diagnostic on its own, as it can raise in several cancers, rheumatologic, gastrointestinal, and cardiovascular conditions, and infections (Windgassen et al. 2011). Elevation of CRP (as determined by a high-sensitivity CRP assay or hs-CRP) has a strong association with elevated risk of cardiovascular disease and stroke (Emerging Risk Factors Collaboration et al. 2010).

Eicosanoids. The cytokine factors mentioned above (interleukins, TNF-α) are "long-distance messages". They are produced by cells at the site of inflammation and released into the blood, carrying information about the inflammatory response throughout the body. In contrast, eicosanoids are "local" messages; they are produced by cells that are proximal to the site of inflammation, and are meant to travel short distances (locally within the same organ, to neighboring cells, or sometimes only to different parts of the same cell) in order to elicit immune defenses (Luo et al. 2011). There are several families of eicosanoids (including prostaglandins, prostacyclins, leukotrienes, and thromboxanes) that are created by most cell types in all major organ systems. Aside from their roles in inflammation (and anti-inflammation), prostaglandins have a variety of functions in cell growth, kidney function, digestion, and the constriction and dilation of blood vessels. Thromboxanes are important mediators of the blood clotting process. Pro-inflammatory leukotrienes are important for recruiting and activating white blood cells during inflammation, and are best studied for their role in airway constriction and anaphylaxis.

Cells produce eicosanoids using unsaturated fatty acids that are part of their cell membranes. The fatty acid starting materials for eicosanoid synthesis are the essential fatty acids linoleic acid (omega-6) and its derivative arachidonic acid (AA); and alpha-linolenic acid (an omega-3) and its derivatives eicosapentaenoic acid (EPA) and *docosahexaenoic* acid (DHA). While generalizations about roles of these fatty acids in eicosanoid synthesis should be approached cautiously, the most potent inflammatory eicosanoids are produced from omega-6 fatty acids (linoleic and arachidonic acids). Diets high in omega-3 fatty acids are associated with lower biomarkers of inflammation and cardiovascular disease risk; proposed mechanisms include the production of less inflammatory or anti-inflammatory eicosanoids and through the cyclooxygenase and lipoxygenase enzymes (see below) (Serhan et al. 2001).

Cyclooxygenases and Lipoxygenases. The eicosanoids (above) require several enzymatic steps to be synthesized from unsaturated fatty acids; the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes catalyze the first steps in these reactions. Cyclooxygenases initiate the conversion of omega-3 and omega-6 derivatives into one of the many prostaglandins or thromboxanes. The interest in COX enzyme metabolism comes from the fact that its inhibition leads to decreased prostaglandin synthesis, and therefore a reduction in inflammation, fever, and pain. The analgesic and anti-inflammatory activity of aspirin and the non-steroidal anti- inflammatory drugs (NSAIDS, like ibuprofen and naproxen) is due to their inhibition of COX enzymes. There are two COX enzymes with well-defined roles in humans (COX-1 and COX-2). COX-2 has the most relevance to the inflammatory process: it is normally inactive, but is turned on during inflammation and stimulates this process of inflammation by creating pro-inflammatory prostaglandins and thromboxanes.

Lipoxygenases convert fatty acids into proinflammatory *leukotrienes*, important local mediators of inflammation. Several potent inflammatory leukotrienes are produced by 5-LOX in mammals. Lipoxygenase enzymes, and the pro-inflammatory factors they produce, have a fundamental role in the inflammatory process by aiding in the recruitment of white blood cells to the site of inflammation. They also stimulate local cells to produce cytokines, which amplifies the inflammatory response (Luo et al. 2011). Thus, LOX enzymes may be involved in a wide variety of inflammatory conditions, and represent an additional target for anti-inflammatory therapy

Diseases Associated with Chronic Inflammation

Cardiovascular diseases (CVD). Inflammation is an integral part of atherosclerosis (recall that

oxidized low-density lipoprotein cholesterol stimulates the inflammatory response). Circulating inflammatory cytokines are predictive of peripheral arterial disease, heart failure, atrial fibrillation, stroke, and coronary heart disease (Singh et al. 2011, Emerging Risk Factors Collaboration et al. 2010).

Cancer. Several studies have established links between chronic low-level inflammation and many types of cancer, including lymphoma, prostate, ovarian, pancreatic, colorectal and lung (Aggarwal et al. 2006).(Kundu et al. 2008) There are several mechanisms by which inflammation may contribute to carcinogenesis, including alterations in gene expression, DNA mutation, epigenetic alterations, promotion of tumor vascularization, and the expression of pro-inflammatory cytokines that have roles in cancer cell proliferation (Kundu et al. 2008, Balkwill 2009)

Diabetes. The infiltration of macrophages into fat tissue and their subsequent release of pro-inflammatory cytokines into circulation occur at a greater rate in type II diabetics than in non-diabetics (Pickup et al. 2000, Nappo et al. 2002, Ortega Martinez de Victoria et al. 2009). Pro-inflammatory cytokines clearly decrease insulin sensitivity (Bastard et al. 2006).

Age-related macular degeneration (AMD). An evaluation of 11 population-based studies encompassing over 41,000 patients demonstrated a clear association between elevated serum CRP levels (> 3 mg/L) and the incidence of late onset AMD (Hong et al. 2011). The risk of AMD in these high-CRP patients was increased over 2-fold compared with patients with CRP levels < 1 mg /L.

Chronic kidney disease (CKD). The chronic, low-grade inflammation in CKD can lead to the retention of several pro-inflammatory molecules in the blood (including cytokines, AGEs, and homocysteine) (Glorieux et al. 2009). The reduced excretion of pro-inflammatory factors by the diseased kidney can accelerate the progression of chronic inflammatory disturbances elsewhere in the body, such as the cardiovascular system.

Osteoporosis. Inflammatory cytokines (TNF-α, IL-1β, IL-6) are involved in normal bone metabolism. Osteoclasts, the cells that break down (resorb) bone tissue, are a type of macrophage and can be stimulated by pro-inflammatory factors. Systemic elevations in pro-inflammatory cytokines push bone metabolism towards resorption, and have been observed to induce bone loss in persons with periodontal disease, pancreatitis, inflammatory bowel disease, and rheumatoid arthritis (Cao 2011). An increase in the levels of inflammatory cytokines is also a mechanism by which menopause stimulates bone loss.

Depression. There is a small, but significant association between elevated IL-6 and CRP in depressed patients, which has been observed in many population studies (Dantzer 2012). It is unclear whether inflammation leads to stress or vice versa, and there is data supporting both hypotheses (Gimeno et al. 2009) (Copeland et al. 2012).

Cognitive decline. Several observational studies have linked chronic low-level inflammation in older adults to cognitive decline and dementia, including vascular dementia and Alzheimer's disease (Singh et al. 2011). One study found that people with the highest CRP and IL-6 levels (> 2.4 pg/mL) had a ~30-40% increased risk of cognitive decline compared to those with the lowest levels (< 1.4 pg/mL). (Yaffe et al. 2003). Inflammatory markers can be elevated before the onset of cognitive dysfunction, indicating their potential relevance as a prognostic tool in high-risk individuals (Singh et al. 2011).

Others. Elevations in circulating inflammatory cytokines are associated with several other conditions, both inflammatory (rheumatoid arthritis, IBD/Crohn's disease, pancreatitis) and non-inflammatory (anemia, fibromyalgia, frailty, sacropenia/cachexia/muscle wasting) (Kaser et al. 2011) (Jha et al. 2009) (Ferrucci et al. 2010, Kadetoff et al. 2011, Rolland et al. 2011). Again, whether inflammation incites these conditions or results from them is unclear, and requires further investigation.

Conventional Medicine Typically Overlooks Chronic Inflammation

Chronic inflammation or para-inflammation is generally not treated on its own by mainstream physicians. Interventions in conventional medicine are usually only undertaken when the inflammation occurs in association with another medical condition (such as arthritis). Currently, conventional preventive medical approaches to inflammation are limited to the use of CRP to predict cardiovascular disease in high-risk subjects, and the prophylactic use of drugs like aspirin to inhibit the inflammatory cascade linked to thrombosis (uncontrolled blood clotting). Indeed, the potentially asymptomatic nature of low grade inflammation is such that elevations of pro-inflammatory cytokines may progress undetected for some time, only being discovered after they have had time to cause enough cellular damage to produce disease symptoms. As future studies solidify the association between inflammatory mediators and different diseases, early detection of cytokine aberrations and anti-inflammatory therapy to reduce disease risk may gain more mainstream acceptance.