

Reducing Pain and Inflammation Naturally - Part IV: Nutritional and Botanical Inhibition of NF-kappaB, the Major Intracellular Amplifier of the Inflammatory Cascade. *A Practical Clinical Strategy Exemplifying Anti-Inflammatory Nutrigenomics*

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Abstract: Modulation of genetic expression by the skillful use of dietary, nutritional, and botanical interventions is clearly the leading edge of modern nutritional practice. Thus, familiarity with the concepts and implementation of “nutrigenomics” must become incorporated into the clinical skill set of chiropractic and naturopathic physicians. This article focuses on the nutritional and botanical inhibition of the primary “amplifier of inflammation” known as nuclear transcription factor kappaB (NF-kappaB). From both clinical and pharmacological standpoints, the safe and effective inhibition of NF-kappaB is considered a major therapeutic goal for the prevention and treatment of conditions associated with an upregulated inflammatory response, namely diabetes, arthritis, cancer, autoimmunity, and the aging process in general. This article introduces concepts and terminology that will facilitate the effective clinical implementation of a nutritional protocol aimed at relieving excess inflammation by inhibiting NF-kappaB.

INTRODUCTION

New research is showing that many diseases are associated with inappropriate activation of nuclear transcription factor kappaB, generally referred to as NF-kappaB. Inhibition of NF-kappaB is now a major therapeutic goal in the treatment and prevention of a wide range of illnesses, including cancer, arthritis, autoimmune diseases, and neurologic illnesses such as Alzheimer’s and Parkinson’s disease.¹ While the development and use of drugs that inhibit NF-kappaB will take several years of additional research and will likely be associated with numerous adverse effects and exorbitant expense, the nutritional and botanical inhibition of NF-kappaB is available to us immediately with proven safety and near-universal affordability. This paper will take readers beyond the benefits which can be obtained with the health-promoting diet², combination fatty acid therapy³, and anti-inflammatory and analgesic nutrients and botanicals⁴ that were described in the first three articles in this series.

THE BIOCHEMISTRY OF INFLAMMATION: FROM NF-KAPPAB TO EICOSANOIDS

The process of inflammation may be said to begin with the translation of an environmental trigger into a biochemical signal that initiates the inflammatory pathway. Proinflammatory environmental triggers can include injury, radiation, infection, oxidative stress, and certain foods, particularly those high in fat and those with a high glycemic index (ie, “simple sugars”), as well as vitamin D deficiency. Regardless of the original locus or etiology, each of these stimuli may lead to activation of the NF-kappaB cascade, which is a major pathway for the amplification of inflammatory processes.⁵

As a ubiquitous nuclear transcription factor that promotes the activation of genes that encode for inflammatory

mediators and enzymes, NF-kappaB can be thought of as the major intracellular “amplifier” which ultimately increases the production of the direct mediators of inflammation such as cytokines, prostaglandins, leukotrienes, nitric oxide and other reactive oxygen species (“free radicals”). The process of inflammation begins when two subunit proteins—p50 and p65—merge in the cytoplasm to form NF-kappaB, which is kept in an inactive state by inhibitor kappaB (IκB). When triggered by any of the common stimuli listed above, IκB is phosphorylated and destroyed by inhibitor kappaB kinase (IKK). The destruction of IκB allows NF-kappaB to move into the nucleus of the cell where it binds with DNA and activates genes encoding for inflammatory responses. These genes then elaborate their inflammatory products such as interleukin-1 (IL-1), IL-6, tumor necrosis factor, and the proinflammatory destructive enzymes including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), the lipoxygenases (LIPOX), and the matrix metalloproteinases (MMP) including collagenase and gelatinase, which destroy connective tissue. Nitric oxide synthase catalyses the formation of nitric oxide (NO-), which plays an important role in the development of peripheral osteoarthritis⁶ and spinal disc degeneration⁷ via oxidative destruction of articular tissues. Cyclooxygenase transforms arachidonic acid into prostaglandins and thromboxanes, which recruit leukocytes to the area of inflammation, exacerbate edema, sensitize peripheral neurons to increased pain perception, and ultimately facilitate the liberation of proteinases, such as matrix metalloproteinases, which destroy joint structures. Present in several isoforms, the lipoxygenase enzyme acts on arachidonic acid to produce leukotrienes that also increase inflammation, joint destruction, and production of MMP. Overall, this same inflammatory response contributes to the genesis and perpetuation of numerous inflammatory disorders, such as osteoarthritis, cancer, rheumatoid arthritis and other autoimmune diseases, and

Figure 1.
The creation and activation of NF-kappaB—a crucial step in the amplification of proinflammatory gene expression.
 Adapted from Vasquez A. *Integrative Orthopedics. (Optimal-HealthResearch.com): 2004*

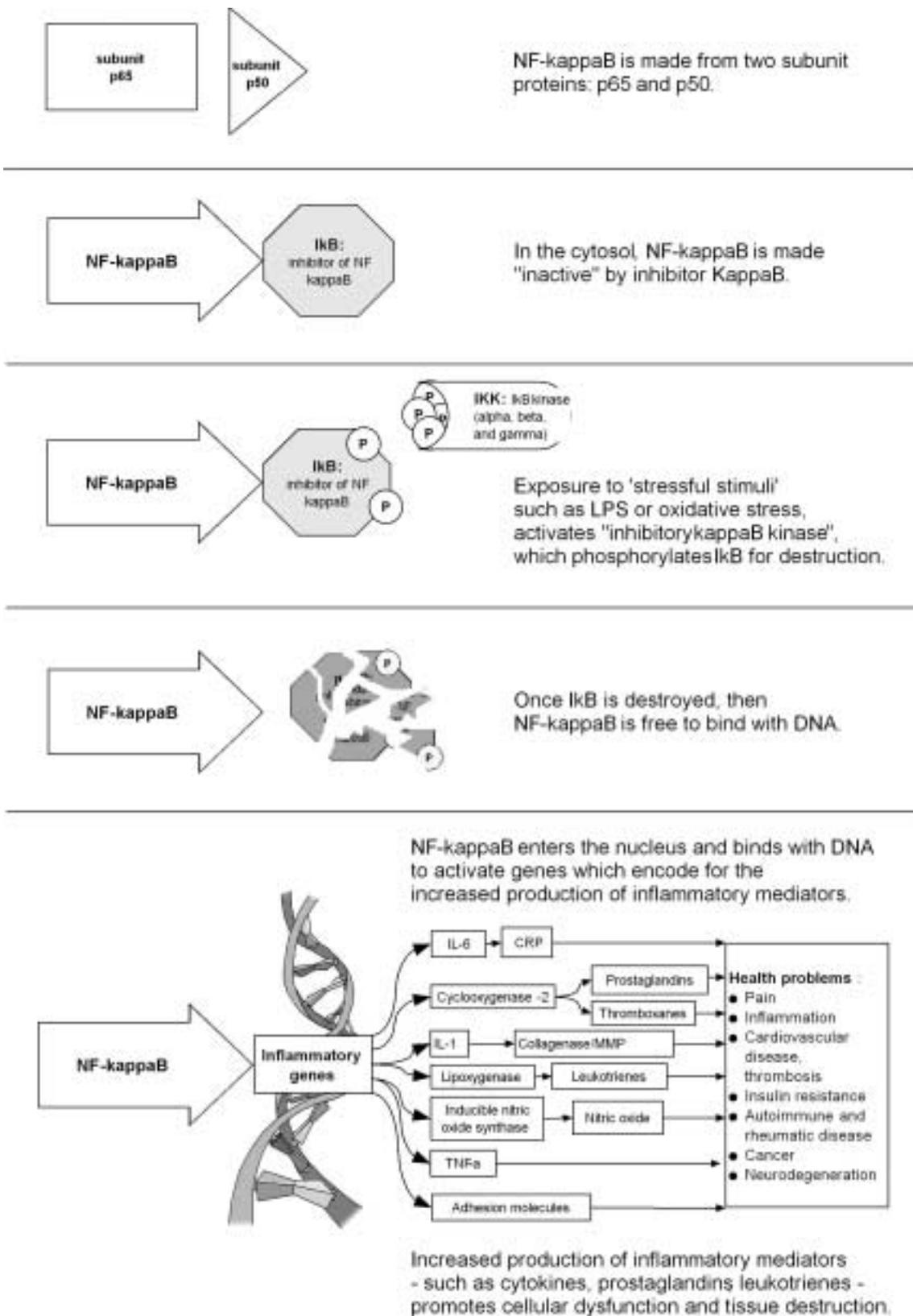
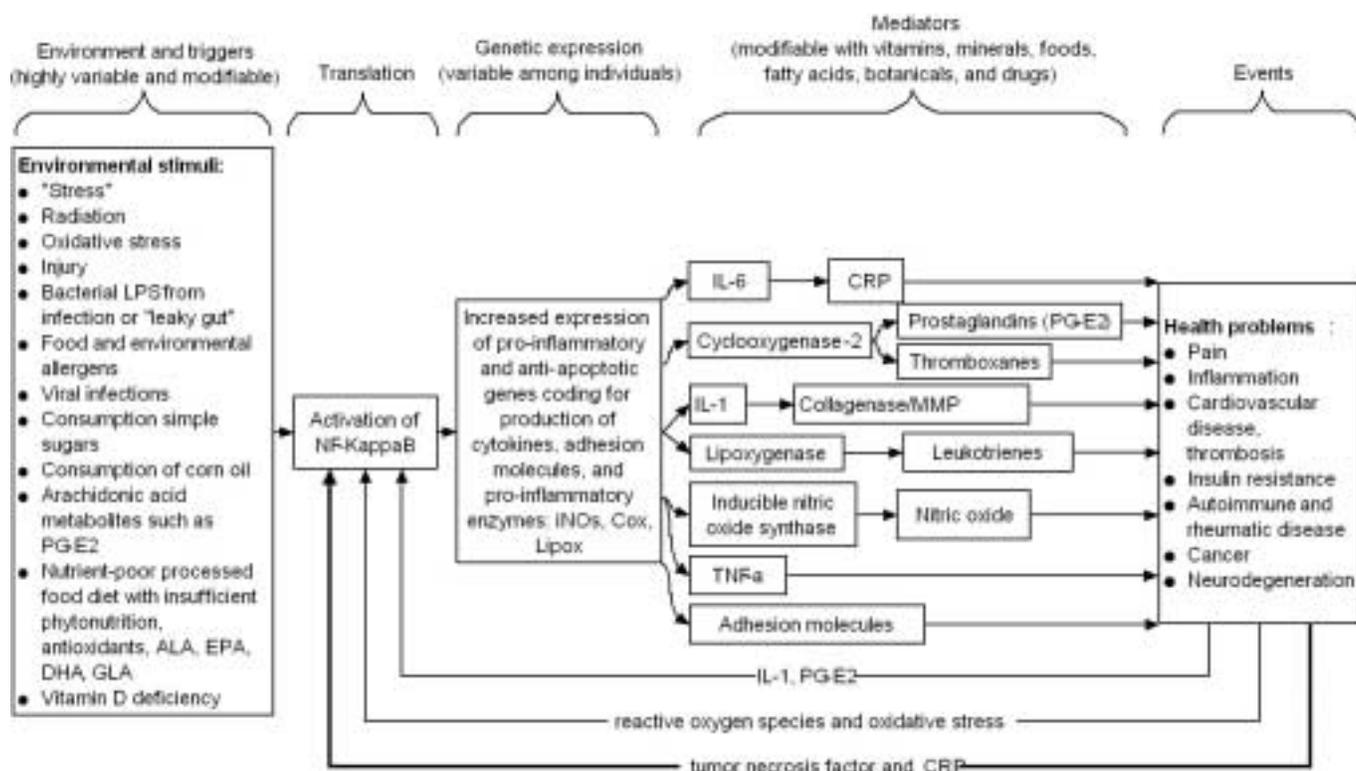


Figure 2. Translation of environmental traumas into biochemical inflammation. Note the self-perpetuating “vicious cycle” where inflammatory mediators promote additional inflammation via activation of NF-kappaB. Adapted from Vasquez A. *Integrative Orthopedics*. (OptimalHealthResearch.com): 2004



essentially all conditions associated with pain and inflammation. This process of NF-kappaB activation and modulation of genetic expression is illustrated in Figures 1 and 2.

FROM BIOCHEMICAL EFFECTS TO CLINICAL CONSEQUENCES

Activation of NF-kappaB leads to the elaboration of mediators that damage tissues and contribute to the clinical manifestations of poor health. IL-6 stimulates production of C-reactive protein (CRP), which is a sensitive serum marker of inflammation (such as in osteoarthritis and rheumatoid arthritis) and is associated with an increased risk of cardiovascular disease, progressively deteriorating health and “rapid biological aging” in men and women.^{8,9} INOS increases production of the free radical nitric oxide which is elevated in degenerating joints⁶ and spinal discs⁷ and which contributes directly to joint destruction via oxidation of articular tissues.¹⁰ COX-2 is responsible for the conversion of arachidonic acid to prostaglandins, several of which increase the perception of pain by sensitizing peripheral nociceptors¹¹ and by a central hyperalgesic effect¹² and by promoting destruction of articular structures by increasing

elaboration of proteolytic enzymes, variously named collagenases, gelatinases, and matrix metalloproteinases.¹³ Similarly, LIPOX catalyzes the conversion of arachidonate to leukotrienes, which promote swelling, inflammation, chemotaxis, and tissue destruction via increased release of proteolytic enzymes. In their anti-inflammatory roles, LIPOX and COX act on GLA for the production of the anti-inflammatory 15-HETrE and prostaglandin E-1, respectively, as well as on EPA and DHA for the production of anti-inflammatory prostaglandins, leukotrienes, docosatrienes, and resolvins as discussed previously.³ Our discussion of the mechanisms of anti-inflammatory nutritional interventions must also include the phytonutritional activation of peroxisome proliferator-activated receptors (PPARs), since fatty acids and selected botanical medicines exert their actions at least in part by activation of PPAR-alpha and PPAR-gamma, which then mediate health-promoting and clinically significant anti-inflammatory effects. As fatty acid receptors that influence genetic expression via suppression of NF-kappaB as well as via NF-kappaB-independent pathways, PPARs when moderately activated induce numerous beneficial physiologic responses, including direct and indirect anti-inflammatory, anti-cancer, and cardioprotective effects.¹⁴⁻¹⁶

NUTRIGENOMICS: MODULATION OF GENETIC EXPRESSION VIA INTERVENTIONAL NUTRITION

The study of how dietary components and nutritional supplements influence genetic expression is referred to as “nutrigenomics” or “nutritional genomics” and has been described as “the next frontier in the postgenomic era.”¹⁷ Various nutrients have been shown to modulate genetic expression and thus alter phenotypic manifestations of disease by upregulating or downregulating specific genes, interacting with nuclear receptors, altering hormone receptors, and modifying the influence of transcription factors, such as proinflammatory NF-kappaB and the anti-inflammatory peroxisome-proliferator activated receptors (PPARs). Indeed, the previous view that nutrients only interact with human physiology at the metabolic/post-transcriptional level must be updated in light of current research showing that nutrients can, in fact, modify human physiology and phenotype at the genetic/pre-transcriptional level.

Fatty acids and their end-products modulate genetic expression in several ways, as these examples will illustrate. In general, n-3 fatty acids decrease inflammation and promote health while n-6 fatty acids (except for GLA, which is generally health-promoting) increase inflammation, oxidative stress, and the manifestation of disease. Corn oil, probably as a result of its high LA content, rapidly activates NF-kappaB and thus promotes tumor development, atherosclerosis, and elaboration of pro-inflammatory mediators such as TNF α .¹⁸⁻²⁰ Similarly, arachidonic acid increases production of the free radical superoxide approximately 4-fold when added to isolated Kupffer cells *in vitro*. Prostaglandin-E2 is produced from arachidonic acid by cyclooxygenase and increases genetic expression of cyclooxygenase and IL-6; thus, inflammation manifested by an increase in PG-E2 leads to additive expression of cyclooxygenase, which further increases inflammation and elevates C-reactive protein.²¹ Some of the unique health-promoting effects of GLA are nutrigenomically mediated via activation of PPAR-gamma, resultant inhibition of NF-kappaB, and impairment of estrogen receptor function.^{22,23} Supplementation with ALA leads to a dramatic reduction of prostaglandin formation in humans²⁴, and this effect is probably mediated by downregulation of proinflammatory transcription, as evidenced by reductions in CRP, IL-6, and serum amyloid A.²⁵ EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation and thus reducing elaboration of proinflammatory mediators.^{26,27} EPA also indirectly modifies gene expression and cell growth by reducing intracellular calcium levels, thereby providing an anti-cancer benefit.²⁸ DHA is the precursor to docosatrienes and resolvins which downregulate gene expression for proinflammatory IL-1, inhibit of TNF α ,

and reduce neutrophil entry to sites of inflammation.²⁹ Oxidized EPA activates PPAR-alpha and thereby suppresses NF-kappaB and the activation of proinflammatory genes.^{27,30} Therefore, we see that fatty acids (and other botanicals and nutrients, discussed below) directly affect gene expression by complex and multiple mechanisms, and the synergism and potency of these numerous anti-inflammatory nutraceuticals supports the rationale for the use of nutrition and select botanicals for the safe and effective treatment of inflammatory disorders.

NATURAL AND SYNERGISTIC INTERVENTIONS THAT INHIBIT NF-KAPPAB

This section efficiently reviews several of the more powerful nutritional and botanical treatments which have been shown to inhibit NF-kappaB. Using these treatments in combination provides additive and synergistic benefits compared to using one treatment at a time.

- **Vitamin D:** Vitamin D has potent anti-inflammatory and pain-relieving benefits in patients with musculoskeletal pain, as previously reviewed in this Journal¹⁴ and elsewhere.^{31,32} Impressively, vitamin D also modulates genetic transcription, as evidenced by its ability to reduce activation of NF-kappaB. Although 25-hydroxyvitamin D has limited biological activity, its more active metabolite, 1-alpha,25-dihydroxyvitamin D3 (1,25-(OH)2-D3) can inhibit NF-kappaB activity in human cells.^{33,34} Thus, it is not surprising that clinical studies in patients with critical illness and multiple sclerosis have shown an anti-inflammatory benefit from vitamin D. Vitamin D supplementation can reduce inflammation by 23% as objectively assessed with C-reactive protein levels.³⁵
- **Curcumin from *Curcuma longa* (“Turmeric”):** Turmeric is an ancient spice that has been used for thousands of years to add flavor and color to food. Although *in vitro* tests and animal studies have suggested that the active components related to curcumin may have potential as powerful agents against human diseases, most researchers and reporters have failed to realize that—in humans—curcumin is very poorly absorbed. Even when curcumin powder is administered in doses as high as 2,000 mg, there is no appreciable increase in serum levels in humans. However, when curcumin is coadministered with piperine, which increases intestinal absorption and reduces enterohepatic detoxification, serum levels of curcumin increase by 2,000% in humans.³⁶ Piperine is derived from *Piper nigrum*, also commonly known as black pepper, a spice found in nearly every kitchen in the

world. Piperine enhances absorption and reduces clearance of some drugs such as theophylline (detoxified by CYP3A4 and CYP1A2) and propranolol (detoxified by CYP2D6); this combination of effects (e.g., enhanced absorption and reduced clearance) may require dosage modification for numerous drugs. No adverse reactions have been reported with doses of piperine up to 15 milligrams per day.³⁷ Pregnant women and nursing mothers should generally avoid piperine supplementation.

- **Lipoic acid:** As a fat-soluble and water-soluble antioxidant with clear biologic activity, it is not surprising that lipoic acid is also noted to inhibit NF-kappaB activity in a dose-dependent manner.³⁸
- **Green tea extract:** Epigallocatechin gallate from green tea is an effective inhibitor of IKK activity. Thus, green tea extract inhibits activation of NF-kappaB. This may explain, at least in part, some of the reported anti-inflammatory and anticancer effects of green tea.³⁹
- **Rosemary:** Carnosol in rosemary inhibits NF-kappaB activation, and this is a likely mechanism of its anti-inflammatory and chemopreventive action.⁴⁰
- **Grape seed extract (GSE):** GSE is a potent antioxidant that has been shown to inhibit NF-kappaB.⁴¹
- **Propolis (a source of caffeic acid phenethyl ester):** Caffeic acid phenethyl ester (CAPE) is an anti-inflammatory component of propolis (honeybee resin) that is a specific inhibitor of NF-kappaB.⁴² CAPE has shown clinical benefit in the treatment of asthma, which is the prototype of chronic airway inflammation.⁴³ As with all bee products, allergy to propolis has been reported and may be more common in patients with a history of allergy to honey or other bee products.
- **Resveratrol:** Resveratrol shows anticarcinogenic, anti-inflammatory, and growth-modulatory effects which are due in part to the inhibition of NF-kappaB.⁴⁴ In fact, according to recent *in vitro* research, resveratrol and quercetin inhibit NF-kappaB more powerfully than the glucocorticosteroid, dexamethasone.⁴⁵ Further support for an anti-inflammatory benefit from resveratrol comes from research showing that resveratrol pretreatment reduces elaboration of COX-2 following administration of the proinflammatory agent, phorbol ester.⁴⁶ This effect is almost certainly a reflection of the ability of resveratrol to inhibit NF-kappaB and thereby reduce transcription of proinflammatory genes.

- **Phytolens (a patented extract from legumes):** Phytolens is a patented polyphenolic extract from lentils. Published experimental research has documented the *in vivo* antioxidant activity of Phytolens against superoxide and other reactive oxygen species.⁴⁷ Anecdotal reports have shown an anti-inflammatory benefit.

CONCLUSION AND CLINICAL IMPLEMENTATION

Inflammation is a destructive and self-perpetuating process wherein activation of NF-kappaB leads to the elaboration of proinflammatory mediators, several of which then lead to a cyclic, positive-feedback upregulation of NF-kappaB. In patients who require a rapid-onset anti-inflammatory benefit, or those who have not adequately responded to the dietary, fatty acid, and joint-supporting interventions described previously^{2-4,32}, intervention with the above-mentioned botanicals and nutrients can lead to efficient and objective reductions in inflammation. Using these natural treatments *in combination* helps to safely reduce activity of NF-kappaB and the resultant inflammation, thus promoting the restoration of homeostasis, the alleviation of pain, and a reduction in joint inflammation and degeneration.

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