

## What Is NFkB? It Could Kill You

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### The Saga of Inflammation

Earlier this year, I completed a six-part series on how diet drives inflammation, pain, subluxation and a host of diseases, including heart disease, cancer and Alzheimer's.\* Nearly all of the degenerative diseases are driven by chronic subclinical inflammation; essentially, nearly every condition that walks into a doctor's office is driven, at least in part, by inflammation.

The old view of inflammation is that it represents the healing response. This is true, to a point; however, once inflammation, becomes chronic, it becomes a disease. You will not find a statement as clear as this in typical physiology books, or even in pathology books. However, in pathology texts, we are led to believe that chronic inflammation plays a role in promoting the disease process. In journal articles, we are given more precise statements. Consider the following:

"Recent studies on diseases which involve insulin insensitivity (e.g. obesity, type 2 diabetes and atherosclerosis) also show increased cytokine production and markers of inflammation. Evidence at present favours chronic inflammation as a trigger for chronic insulin insensitivity, rather than the reverse situation."<sup>1</sup>

You will not find this type of statement in any physiology or pathology book anytime soon. Why? I don't know. Nonetheless, we can see that inflammation is definitively viewed as a driver of chronic disease.

### The Reduction of Inflammation

In recent years, a massive volume of literature has supported the view that we need to halt chronic inflammation and its induction. Aspirin, NSAIDs and corticosteroids have been the main medical weapons against inflammation. These days, COX2 inhibitors are also being used.

Pharmacology texts tell us that aspirin, NSAIDs, and COX2 inhibitors act to reduce inflammation by blocking the cyclooxygenase enzyme that converts arachidonic prostaglandin E-2 (PGE2). In other words, these drugs inhibit inflammation by blocking PGE2. Corticosteroids work higher up the chain, inhibiting phospholipase A2, which inhibits arachidonic acid release from phospholipids in the cell membrane. These mechanisms have been known about for a long time. For example, in 1971, John Vane discovered that aspirin inhibits the COX enzyme.

In more recent years, the study of inflammation has gone deeper into the cell, to the point that cell-signaling molecules have been identified which stimulate genes that induce the expression of the COX enzyme. As it turns out, aspirin, NSAIDs, and corticosteroids can inhibit certain cell signaling molecules, such as nuclear factor kappa binding (NFkB) - which reduces inflammation.

On the natural end of the treatment spectrum, various botanicals have anti-inflammatory effects that work in the same manner as these drugs, except their actions are not as pronounced. Ginger and curcumin are the most well-known substances that possess significant anti-inflammatory

actions.

## Nuclear Factor Kappa B

NFkB is the "big cheese" cell-signaling molecule for inflammation; its activation induces the expression of COX-2, which leads to tissue inflammation. "Intriguingly, the expression of the COX-2-encoding gene, believed to be responsible for the massive production of prostaglandins at inflammatory sites, is transcriptionally regulated by NFkB."<sup>2</sup>

NFkB resides in the cytoplasm of the cell and is bound to its inhibitor. Injurious and inflammatory stimuli, such as free radicals, release NFkB from the inhibitor. NFkB moves into the nucleus and activates the genes responsible for expressing COX-2. Research has demonstrated that aspirin, NSAIDs, and corticosteroids can inhibit the activation of NFkB, which is why people derive relief from these drugs. Problems arise due to their nasty side-effects, which means that alternative ways need to be pursued to reduce NFkB activity.

As mentioned earlier, free radicals are examples of substances that activate NFkB. Cytokines such as interleukin-1 (IL-1) can also stimulate NFkB.<sup>2</sup> Not surprisingly, antioxidants can reduce the activation of NFkB, including green tea polyphenols; resveratrol from red wine; vitamins C and E; curcumin; and glutathione.<sup>2</sup> Whenever you see glutathione, you need to think of the substances that maintain glutathione in its active state, which includes supplements such as lipoic acid and coenzyme Q10.<sup>3</sup>

In all likelihood, the family of flavonoids and carotenoids found in fruits and vegetables that have antioxidant functions is capable of reducing free-radical activation of NFkB. So, our approach to keeping NFkB at bay should be a fruit- and vegetable-based diet that includes green tea, red wine, and antioxidant supplements.

Fatty acids (FAs) also need to be considered. The anti-inflammatory omega-3 FAs reduce NFkB activity,<sup>4,5</sup> which means we need to reduce our grain, seed, and related oil intake. Omega-3 FAs also reduce IL-1,<sup>6</sup> which is an activator of NFkB.<sup>2</sup> Omega-3 fatty acids are found in green vegetables, most fish, wild game, and grass-fed meat. (See [www.texasgrassfedbeef.com](http://www.texasgrassfedbeef.com).) Supplementing with 1-2 grams of EPA/DHA from fish oil is also a good idea.

We must also be cognizant of glycemic regulation in controlling NFkB.<sup>7</sup> An assessment of Type 1 diabetic patients found that inefficient glycemic control resulted in increases in NFkB activity in white cells - which results in inflammation. This means that, as alluded to earlier, inflammation causes diabetes,<sup>3</sup> and the diabetic state promotes inflammation.<sup>7</sup> It was determined that HbA1c and NFkB were correlated with each other, and also with hyperglycemia and lipid peroxidation.<sup>7</sup>

## Diseases Driven by NFkB

We want to reduce the inappropriate activation of NFkB because it can drive so many seemingly unrelated diseases. We don't typically think of asthma and neurodegenerative diseases as having similar etiologies; however, NFkB plays a role in each disease. In fact, NFkB promotes asthma; neurodegeneration; ischemia/reperfusion injury; hepatitis; glomerulonephritis; inflammatory bowel disease; rheumatoid arthritis; and probably most other diseases driven by inflammation,<sup>2</sup> including the subluxation complex.<sup>8,9</sup> Consider that Faye's original model of the subluxation complex included

an inflammatory component.

On a more lethal note, I searched MEDLINE for articles related to cancer and NFkB; 1,773 appeared. One paper stated that NFkB is strongly linked to inflammatory and immune responses, regulation of cell proliferation and apoptosis, suggesting its role in tumor development and many other diseases, including atherosclerosis.<sup>10</sup> I suggest we adopt an anti-inflammatory diet and give ourselves a nutritional adjustment.

### References

1. Grimble RF. Inflammatory status and insulin resistance. *Curr Opin Clin Nutr Metab Care* 2002;5:551-9.
2. D'Acquisto F, May MJ, Ghosh S. Inhibition of nuclear factor kappa B (NF\_κB): an emerging theme in anti-inflammatory therapies. *Molec Interv* 2002;2:22-35.
3. Sen CK, Packer L. Thiol homeostasis and supplements in physical exercise. *Am J Clin Nutr* 2000;72(2 Suppl):653S-69S.
4. Lo CJ, Chiu KC, Fu M, Lo R, Helton S. Fish oil decreases macrophage tumor necrosis factor gene transcription by altering the NF kappa B activity. *J Surg Res* 1999;82(2):216-21.
5. Novak TE, Babcock TA, Jho DH, Helton WS, Espat NJ. NF-kappa B inhibition by omega -3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. *Am J Physiol Lung Cell Mol Physiol* 2003;284(1):L84-9.
6. Simopoulos AP. Essential fatty acids in health and chronic disease. *Am J Clin Nutr* 1999;70(3 Suppl):560S-569S.
7. Hofmann MA, Schiekofer S, Kanitz M, et al. Insufficient glycemic control increases nuclear factor\_κB binding activity in peripheral blood mononuclear cells isolated from patients with type 1 diabetes. *Diabetes Care* 1998; 21:1310-16.
8. Seaman DR. Joint complex dysfunction, a novel term to replace subluxation/subluxation complex: etiological and treatment considerations. *J Manipulative Physiol Ther* 1997;20(9):634-44.
9. Seaman DR. The diet-induced proinflammatory state: a cause of chronic pain and other degenerative diseases? *J Manipulative Physiol Ther* 2002;25 (3):168-79.
10. Ignatowicz E, Baer-Dubowska W. Resveratrol, a natural chemopreventive agent against degenerative diseases. *Pol J Pharmacol* 2001;53(6):557-69.

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Editor's note: Dr. Seaman's six-part series on diet and inflammation is available online at [www.chiroweb.com/archives/20/21/18.html](http://www.chiroweb.com/archives/20/21/18.html).

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