

COVER STORY

Inflammation and the aging brain

By Dale Kiefer



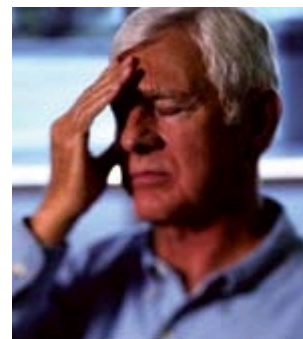
Inflammation is now thought to play a role in pathological conditions ranging from anemia and allergy to coronary heart disease, psoriasis and even stroke. From inflamed gums that may contribute to cardiovascular disease, to playing a crucial role in fanning the flames of cancer cell growth, inflammation has been implicated in many more diseases than was previously believed.

Recently, inflammation has also been recognized as playing a central role in the debilitating cognitive decline that characterizes neurological disorders such as Alzheimer's disease and vascular dementia. Although mental decline and memory loss have long been considered inevitable hallmarks of old age, new research suggests that such inflammation/age-associated decline is avoidable. Indeed, findings reported by some scientists suggest that early intervention in low-grade inflammation may offer some protection against these dreaded brain diseases.

The many guises of inflammation

Inflammation is as familiar as an overworked muscle, and as common as your latest sunburn. Parents who have agonized over a child's escalating fever know that inflammation occasionally transcends the merely annoying to become something far more troubling: Fever that climbs too high for too long can inflict serious, even life-threatening, damage.

But inflammation, including fever, serves a useful purpose in the body. Even sunburn is a result of the body's attempt to repair damage inflicted by ultraviolet radiation. In fact, inflammation is an ingenious adaptation that allows the body to defend against clear and present dangers.



For instance, when virulent bacteria invade, they thrive precisely at the body's normal temperature of 98.6 °F (37 °C). Once established, they pour toxins into the bloodstream, while continuing to proliferate exponentially. The immune system mounts a defense, but cellular defenders may be thwarted or simply overwhelmed. In response, the body turns up the furnace. Sensitive to the slightest temperature increases, pathogens perish. The body wins the battle. Fever breaks and all is well.

This is just one example of inflammation's beneficial nature. But some inflammation goes too far. Fever doesn't always vanquish the invading horde and fade back to a state of disease-free normalcy. Occasionally the cost of battle is too dear and fever damages the very body it is defending. Autoimmune diseases provide another example of inflammation gone awry. The immune system targets the body's own tissues by its inability to differentiate between some of the body's proteins and foreign invaders. In essence, the immune system wages war, against itself. Diseases such as rheumatoid arthritis and lupus erythematosus are the result. Clearly, inflammation can be a double-edged sword.

News from the hot zone

The inflammation of most concern, however, generally goes unnoticed. It is this low-grade chronic inflammation (as opposed to the acute, intense inflammation associated with a healing wound, for instance) that is believed to underlie the most serious neurodegenerative diseases. Huntington's disease, for example, is characterized by chronic brain inflammation caused by the immune system's misguided attempts to eliminate a defective protein that results from a genetic defect. And although their inflammation triggers are different, diseases such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (Lou Gehrig's disease, or ALS) and even multiple sclerosis, are also characterized by chronic inflammation of neural tissues.



Regarding Alzheimer's disease, one research team noted, "Inflammation is becoming increasingly substantiated as a contributor to Alzheimer's disease pathogenesis"¹ For this reason anti-inflammatory drugs, such as the non-steroidal anti-inflammatory drugs (NSAIDs, e.g. aspirin, ibuprofen and acetaminophen) and the newer COX-2-inhibitor class of prescription drugs, are under investigation as therapies for this and other inflammation-related diseases.

Inflammation and the brain

To better understand inflammation's role in disease, it's helpful to comprehend its more benevolent role in keeping the body healthy. Inflammation is the body's response to a perceived threat. In the case of an invasion by bacteria, the immune system correctly identifies the unwelcome entity and attempts to neutralize it. This involves a complex chain of events and may require the cooperation of a variety of specialized cells. Their activity is generally beneficial, but the goal is always the same:

to rid the body of intruders and to dispose of damaged tissue so healing may take place.

Throughout most of the body, cells known as macrophages act as living soldiers, searching for invaders, and then engulfing and neutralizing them. In the brain, supporting cells of the glial family, known as microglial cells, act as scavengers, in much the same fashion as macrophages. They engulf and eliminate dead neurons that have been damaged by injury or illness. Unfortunately, they also secrete harmful neurotoxins and toxic oxygen free radicals in an attempt to neutralize foreign or undesirable substances.²

Regrettably, the inflammatory response is occasionally worse than the stimulus that triggered it in the first place. Even when the original trigger is eliminated, inflammation may become self-perpetuating. Such, apparently, is the case in neurodegenerative diseases such as Alzheimer's, Parkinson's, ALS and multiple sclerosis, which are characterized by a great deal of microglial activity. The presence of activated microglial cells is an indicator of chronic inflammation.^{3,4}

Alzheimer's and inflammation

Much remains to be elucidated regarding the onset and progression of Alzheimer's disease, but it seems clear that an inflammation-provoking protein fragment, a peptide known as amyloid-B, triggers inflammation. Uninterrupted, the inflammation gradually accelerates, killing nerve cells and causing a drastic decline in levels of a vital brain chemical, the neurotransmitter acetylcholine. This downward spiral of neural degeneration commences with the induction of nearly undetectable inflammation, progresses to the erosion of memory, concentration and learning ability and ends with death. Upon demise, Alzheimer's patients display abnormal spaghetti-like neuritic amyloid-B plaques and neurofibrillary tangles. Like a battleground littered with the remains of the combatants, these damaging plaques are associated with reactive microglial cells, and consist of amyloid-B protein fragments, immune system proteins such as interleukin-6 (IL-6) and other components indicating long-term, and ultimately counterproductive, inflammation.⁵

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Microglial cells, which accompany the neuritic plaques of Alzheimer's disease, are normally dormant. They are activated only in response to inflammation, thus their presence is a sure sign of brain inflammation. Although present in large numbers in the brains of patients with degenerative neurological diseases, such as Huntington's⁶ and Alzheimer's diseases, their numbers are also elevated in otherwise healthy elderly individuals. This implies that a certain degree of neuroinflammation is an ordinary result of nothing more than advanced age.² Indeed, some scientists have suggested that cognitive decline begins early in the aging process and is an inevitable result of advancing age.⁷ Controlling inflammation, therefore, could presumably benefit anyone interested in preventing eventual memory loss and cognitive decline.

Dual pathways to inflammation

Just in the last decade, scientists discovered a key enzyme produced by the body in response to inflammatory provocations: cyclooxygenase-2 (better known as COX-2). COX-2 has been identified as an important link in the inflammation cascade. Unlike COX-1, COX-2 is only present in the body during inflammation. Research has revealed that cells convert cell membrane phospholipids to arachidonic acid, which serves as a substrate that gives rise, in turn, to two powerful and potentially damaging classes of inflammation mediators, known as eicosanoids: the prostaglandins and leukotrienes. As one researcher noted, "Arachidonic acid release and production of eicosanoids are prerequisites for inflammation"¹ The eicosanoids are synthesized from arachidonic acid by the action of two enzymes that form the crux of dual inflammatory pathways: cyclooxygenase (COX) and lipoxygenase (5-LOX).

The COX proteins take two forms: COX-1 and COX-2. The actions of COX-1 are generally beneficial. But the activity of COX-2 is generally harmful. COX-2 inserts an oxygen molecule into arachidonic acid to synthesize prostaglandins, which are powerful triggers of pain and inflammation. 5-LOX converts arachidonic acid into inflammatory leukotrienes.



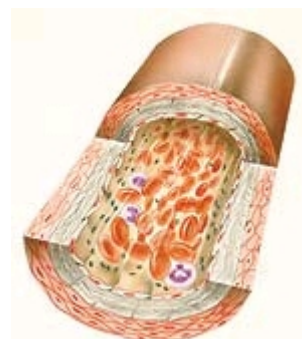
NSAID medications treat inflammation by blocking the activity of both the COX-2 enzyme and its more benevolent sibling, COX-1. But COX-1 is necessary for stomach lining protection; so interfering with COX-1's activity can cause gastric disturbances ranging from simple discomfort to dangerous bleeding ulcers. For this reason the new COX-2-inhibitor class of prescription drugs (e.g. Celebrex and Vioxx) has rocketed to popularity. Their more selective action effectively relieves inflammation while minimizing the distressing side effects that are possible with chronic use of NSAIDs.

Researchers are investigating the possibility that anti-inflammatory agents, such as the COX-2 inhibitors, may provide viable therapy not only for Huntington's, but also for other neuro-degenerative diseases such as Alzheimer's and Parkinson's disease. It's well documented that the COX pathway generates inflammatory prostaglandins. But medical research has largely ignored the potentially damaging effects of 5-LOX, the enzyme that forms the second branch of the dual arachidonic acid inflammation pathways. As a recent study reported, 5-LOX might play a significant role in the pathobiology of aging-associated neuro-degenerative diseases.⁸

5-LOX generates inflammatory leukotrienes, which are known to be potent inflammatory mediators that play a role in allergic reactions. They may also play a role in ischemia and atherosclerosis.⁹ Stroke, traumatic brain injury and Alzheimer's disease have also been linked to the activity of 5-LOX and leukotrienes.² The results of a recent study indicate that blocking COX-2 while ignoring the effects of 5-LOX may be counter-productive. In fact, using COX-2 inhibitors to block the activity of COX-2 may actually cause 5-LOX levels to increase further, making inflammation worse, rather than better.² This "rebound" inflammation is evidently caused by shifting arachidonic acid toward synthesis of damaging leukotrienes through the 5-LOX pathway.

An obvious solution to this problem would be the addition of a drug to the anti-inflammatory regimen that can block 5-LOX. Fortunately, such substances exist, although they have only recently come under scrutiny as complements to far more heavily researched NSAIDs and COX-2 inhibitors.

In one 5-LOX inhibition study, researchers speculated, 'Inhibitors of the two pathways might have additive, or even synergistic neuroprotective effects when used in combination.' By study's end, they had concluded that a 5-LOX inhibitor "significantly



potentiated the effects of three different COX inhibitors.”² Their findings suggest, quite simply, that while anti-inflammatory therapy with COX-inhibitors may be neuroprotective, therapy combining both COX and 5-LOX inhibitors should prove considerably more effective.



The promise of anti-inflammatory therapy

The feedback loops in the brain do not allow for simplistic approaches to the treatment of multi-factorial diseases. Not surprisingly, a recent study in the Journal of the American Medical Association found that COX-2 inhibition alone was ineffective in slowing the progression of clinically diagnosed Alzheimer's disease. It is likely that these results reinforce a growing body of research that dual inflammatory pathway inhibition may be needed to fully realize the promise of anti-inflammatory therapy. While anti-inflammatory therapy may slow progression of some diseases, it may be necessary to begin taking anti-inflammatory agents long before symptoms appear, in order

to prevent or reverse the ravages of neurodegenerative diseases.

References

1. Paris D, et al. AB vasoactivity: an inflammatory reaction. Ann N Y Acad Sci (no date provided) pp.97-108.
2. Klegeris A et al. Cyclooxygenase and 5 lipoxygenase inhibitors protect against mononuclear phagocyte neurotoxicity. Neurobiol of Aging 2002 (23) 787-794.
3. Teismann P, et al. Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. PNAS 2003; 100 (9):5473-5478.
4. Pompl PN, et al. A therapeutic role for cyclooxygenase-2 inhibitors in a transgenic mouse model of amyotrophic lateral sclerosis. FASEB J. 2003; 10.1096/fj.02- 0876fje
5. Scali C, et al. The selective cyclooxygenase-2 inhibitor rofecoxib suppresses brain inflammation and protects cholinergic neurons from excitotoxic degeneration in vivo. Neuroscience 2003; 117:909-919.
6. Sapp et al., Early and progressive accumulation of reactive microglial in the Huntington Disease Brain. Neuropathol Exp Neurol 2001; 60(2): 161-172.
7. Jorm AF, et al. The prevalence of dementia: a quantitative integration of the literature. Acta Psychiatr Scand 1987; 76: 465-479.
8. Uz T, et al. Aging-associated up-regulation of neuronal 5- lipoxygenase expression: putative role in neuronal vulnerability. FASEB 1998; 12: 439-449.
9. Spanbroek R et al. Expanding expression of the 5-lipoxygenase pathway within the arterial wall during human atherogenesis. PNAS 2003; 100:12381243.

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