NSAIDs and Connective Tissue Health

by Liam Bowler

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Introduction

When I was playing sports in high school and college—most often taekwondo, though also skiing, climbing and running—ibuprofen was a daily ritual. My fellow athletes and I took as much of it as we needed to combat the day-to-day inflammatory process of strenuous training. We could train hard, wake up quite sore, and be back to fully functional, or at least close, within half an hour.

Also of particular allure for a college athlete: It didn't need a prescription, and it was cheap. I could take lots of it, and I did: often 1,600 mg a day in peak season. This had no negative repercussion as far as I could tell. My only wariness was around potential gastrointestinal issues, like ulcers, which a few of my athletic heroes had experienced during their many years of high ibuprofen dosage. Other than that, though, I never gave its use much of a second thought.

I also never gave much thought to the constant battle I was having with the inflammatory process, and I feel confident speaking on behalf of my athlete peers that they thought similarly. Our nickname for ibuprofen—"Vitamin I"—speaks to the fullness with which we accepted anti-inflammatories as a natural part of our day-to-day routine. It was like we should be getting it by eating mangoes or something, but we supplemented instead.

In recent years, I have begun questioning such regular use of anti-inflammatory drugs, an intervention that assumes, "Oh, your body is just overreacting." I have become curious about the inflammatory process, and if it has an important purpose many of us have overlooked. That curiosity became the premise of this article, and led me to read up on the inflammatory process and research the literature about inflammation and NSAIDs.

The result is an article not focused on athletes, or even musculoskeletal injury per se, but on the broader and more inclusive topic of the interplay between inflammation and connective tissue health. In this article, I will remind you of some of the properties of musculoskeletal connective tissue and present an explanation of what happens during inflammation. I will draw information gleaned from some recent studies regarding NSAID use and the healing process of traumatized or pathological tissue, discussing the possible implications of cutting that process off. Finally, I will consider the ramifications of using NSAIDs on a regular or daily basis to quell pain and soreness, when its use is not driven by acute injury or disease per se. But first, what exactly are NSAIDs?

NSAIDs and Their Use

Ibuprofen falls under a larger class of drugs known as NSAIDs: non-steroidal anti-inflammatory drugs. The *non-steroidal* part of the name differentiates them from anti-inflammatories that work at an adrenal level; cortisone, a glucocorticoid, is a common example of a steroidal anti-inflammatory. In addition to ibuprofen, NSAIDs include naproxen sodium (like Aleve), aspirin, and a host of prescription drugs, all of which have a similar mechanism of inflammatory intervention, a process we'll review later in this paper.

Their commonplace use goes far beyond my sleepy college town. For the last 30 plus years, NSAIDs have been among the most frequently used drugs in the United States. From 1973 to 1983, for instance, the number of NSAID prescriptions dispensed by retail pharmacies nearly tripled, rising from 28 million to around 70 million by the early 1980s.[1] They are the most widely used painkiller in the world.[2] Even among elite athletes, their use is prevalent: According to random drug testing done at the 2000 Sydney Olympic Games, approximately one in four Olympic athletes reported taking NSAIDs within the past three days.[3]

Connective Tissue

The focus of this paper is on the interplay between inflammation and connective tissue. While technically connective tissue includes blood, in this article I am referring to the musculoskeletal connective tissue—the deep investing fascia, epimysium, endomysium, tendons, ligaments, aponeuroses, intermuscular septa, and bone.

This is the connective tissue that, along with the contractile part of our musculature, bears the enormous force loads we put on our structures. It is the irritation of these tissues that is the primary reason why people, like myself in the days of yore, take anti-inflammatories in the first place.

Before going on, I would like to give a brief nod to other tissues that play a role in the inflammatory process: blood and its innumerable chemical messengers, the nervous system, and the oft forgotten lymphatic system, which shoulders the responsibility for final clean-up. It's certainly worth noting the interconnected nature of these systems, in inflammation or any other bodily process. We can separate our different tissues for the purpose of study or discussion, as I will do here, but functionally speaking, to divorce one system from another and have it represent the whole doesn't work.

Musculoskeletal connective tissue is comprised of various concentrations of cells (like adipose), ground substance, and various fibers (such as elastin and collagen).[4] The fiber that concerns us most is collagen, because of its abundance in the body, its resilience, and its ability to hold strong (like in the fascial thickening in the lower back, to which the gigantic latissimus dorsi attaches, and in the cartilaginous foundation that provides the resilience in our bones). The ability to both stabilize and have properties of fluidity, which collagen readily displays, is called plasticity.[5]

Surrounding the collagen and elastin fibers is the ground substance, a gooey, watery gel that serves as the environment for our cells. This gel's adaptability is of note. According to Tom Myers, "In an active area of the body, [it] changes its state constantly to meet local needs; in a 'held' or 'still' area of the body, it tends to dehydrate to become more viscous, more gel-like, and a repository for metabolites and toxins."[6]

Myers' peek into physiology is an illustration of an often quite intuitive law of the body: Move it or lose it. As Paracelsus said in the 16th century, "There is but one disease, and its name is congestion."[7] We'll proceed with that assumption, that stagnation in the connective tissue makes it less healthy and resilient, while activity and mobility makes it healthier. Let's move on now to the inflammatory process, and see what happens within the connective tissue during inflammation.

The Inflammatory Process, and How Anti-Inflammatories Work

Inflammation is a reaction and quick treatment we have evolved against many of the "the thousand natural shocks that flesh is heir to" (thanks, Hamlet), from infection to chemical poisons to trauma. Its four principle signs are so reliable and unmistakable that Celsus named them 2000 years ago—*rubor, dolor, calor,* and *tumor* (that's redness, pain, heat, and swelling).

Inflammation in response to injury is a local reaction affecting the injured tissue. (People may also take NSAIDs for low-grade, *systemic* inflammation, but here we are discussing local inflammation.) Local inflammation facilitates a pain response through changing the chemical environment, sending out the body's message of *lay off, don't touch, let me heal.* It also creates chemical and spatial changes (swelling) not directly related to increased pain.

Imagine you're strolling around and you sprain an ankle ... you put in a huge session at the gym ... you fall off your trike. Regardless of the traumatic mechanism, the following happens in seconds: macrophages (meaning literally, "big eaters"), which are bred from stem cells for this type of local clean-up, begin producing pro-inflammatory cytokines.[8] Neutrophils and other immune cells migrate via the blood from elsewhere in the body to the interstitial spaces in the traumatized area, where they ingest the pathogens and waste being actively produced. Within cells, signals produced by this group of "first responders" stimulate release of locally acting hormones known as prostaglandins.[9]

The macrophages mentioned earlier are largely responsible for cleaning up the mess, and the pro-inflammatory cytokines are responsible for catabolism of cartilage, i.e. the breaking down of (damaged, at this point) tissue. This complex progression of chemical signals, just touched upon here, leads to the familiar redness, swelling, heat, and pain.

This is a simplified summary, but what is of note now is the presence of both local reactions (i.e., prostaglandins produced within the local tissues) and more systemic ones (i.e., the recruitment of immune cells from their lymphatic storage sites). Anti-inflammatories, as the name would suggest, largely block these processes. NSAIDs intervene at the stage where some of these cytokines signal the body to produce prostaglandins (PGs), among other similar-acting hormones.[10]

This interplay between PGs and the cytokines that signal their production is a sort of feedback loop. The loop, as long as it's on, says to the local tissue, "This isn't time to make anything new; we're in breakdown mode." The rate-limiting mechanism, or one switch on this feedback loop, is the conversion of arachidonic acid to prostaglandin endoperoxide (PGE) by cyclooxygenase (COX).[11]

NSAIDs block cyclooxygenase's production, either primarily COX-2 or both COX-1 and COX-2.[12] Blocking this part of the feedback loop thereby blocks

the production of prostaglandins, along with other messenger molecules in this loop with similar local function.[13]

Prostaglandins behave differently in different tissues; that is, their presence in one area of the body will produce different effects than those produced by their presence in another area. Depending on their locale, they can either stimulate collagen synthesis, or they can do the opposite and promote cartilage re-absorption.[14]

In the conclusion to a study on the effects of NSAIDs on osteoarthritis—one of the diseases in which NSAIDs are often prescribed in the maximally tolerated dose for long-term therapy[15]—the author notes their ill affects. He writes that while "it was hoped that the use of NSAIDs ...would have a disease-modifying effect ... research, unfortunately is showing PGs ... stimulate chondrocyte proliferation and subsequent synthesis of cellular matrix components."[16]

That's the kicker, it seems, of suppressing PGs at one location in the body in order to reduce inflammation: PGs are also responsible for the regeneration of collagen, so this process is also suppressed. This is true not only about creation and reinforcement of connective tissues locally *after* the acute phase of trauma recovery. Off-site tissues are also affected *during* NSAID use; their ability to synthesize collagen is impaired. The same chemicals, then, that cause inflammation and immobilization of an area also seem to play an essential part of the synthesis of the extracellular matrix as a whole.[17] The otherwise-healthy connective tissue's ability to adapt to new stimuli, its plasticity in structure and function, is impaired by long-term NSAID use.

NSAIDs also tend to dehydrate tissue.[18, 19, 20, 21] This news is delivered most commonly as part of a warning that excessive NSAID use can lead to kidney failure. Indeed, that's true,[22] and it is also related to the suppression of local prostaglandins.[23] Long before renal failure, though, we'd be well advised to remember the solid/gel properties of the intercellular ground substance: that the more viscous this material becomes, the less able it is to physically process toxic material and cellular waste. This is true locally at the site of an injury and also more globally throughout the body.

Implications

As prostaglandins are an integral part of connective tissue metabolism, including both the catabolic and anabolic reactions that are part of the inflammatory process, it stands to reason that slowing or blocking this process impedes our connective tissue health.

Indeed, that's what many studies have shown: NSAID use actually inhibits repair of musculoskeletal injuries.[24, 25, 26, 27]

There were no studies I found explicitly examining how NSAIDs affect non-injured or non-pathological connective tissue. The studies that have been done around NSAIDs' role in trauma and pathology, however, should give us pause as to how and when we're doing anything to dampen the inflammatory process.

As a final side note, for this author, the following imagery makes intuitive sense: to dry up a hot, wet world (especially during the acute and sub-acute phases of an injury) is to remove something valuable to the process of healing, the stage of decomposition (which outside our bodies, in nature, needs heat and moisture). In artificially making the tissue environment to our liking through anti-inflammatory use, and much more manageable (i.e., we can still move, and do what we want to do), we mirror a culture largely averse to decomposition and death in general.

Given our natural desire to avoid pain, it also makes sense that we have developed an aversion to inflammation and a ready reach for NSAIDs. But it seems we are suffering because of it; with NSAID use our tissues are less hydrated, less able to efficiently flush out wastes, and less able to heal fully, and research is showing it.

Endnotes

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