

Exercise is Medicine

The anti-inflammatory effects of high intensity exercise

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Exercise is a readily accessible, safe, and inexpensive anti-inflammatory medicine. Inflammation is the body's natural means of stimulating healing, but when continuous and chronic it becomes damaging and detrimental to health. Properly performed exercise releases signaling molecules that stimulate a unique healing response that couples both inflammatory and anti-inflammatory mechanisms to repair, regenerate, and grow tissue stronger. Understanding the history and mechanism behind these effects creates new prescriptive opportunities for exercise. Unlike drugs that have single targets and ignore the web-like interactions in the body, exercise works with the body's innate intelligence to produce broadly beneficial effects that improve whole body function. High intensity short duration movement that is tailored to the individual, uses short rest periods, and engages the whole body may be the chief means of attaining anti-inflammatory effects from exercise.

The human body was designed for activity and evolved with movement. The vast majority of human existence was steeped in the harsh realities of the natural world. Our ancestors did low intensity activity all day every day and were forced to engage in vigorous movement to avoid danger and procure food. This extreme physical reality made injury and infection commonplace. Inflammation produced in response to physical insults was the body's natural protective mechanism for healing.

While inflammation is often thought of as destructive, it is actually a closely orchestrated event that first produces pain, redness, swelling, heat and tissue destruction, but then is followed by repair. Over the millennia, the human body evolved and used acute inflammation to heal, repair, and regenerate itself. Movement was an essential part of this healing and regenerative process. The unique anti-inflammatory effects of movement have been circumvented in the modern era. With the arrival of the industrial and technological revolutions human movement came to a crawl. This left inflammation unchecked by the anti-inflammatory and growth stimulating effects of exercise.

In modern day, the human body is confronted with persistent stress. Along with this stressful lifestyle, humans are no longer dependant on movement and its growth stimulating and healing effects. As a result, acute and controlled inflammation has given way to chronic low level inflammation. This type of inflammation is less detectable by objective or subjective measures making it more insidious in nature. The lifestyle of prehistoric humans had substantial risks, yet their movement patterns kept chronic inflammation at bay. Their exercise patterns worked with inflammation to repair, replace, and regenerate damaged tissue. Without the balancing effects of exercise, inflammation is allowed to smolder at a low level damaging tissue and destroying the quality and quantity of life.

Myokines- muscle-body messengers

Every time the body moves, muscles release signaling molecules that communicate to the rest of the body. The endocrine properties of muscle, like fat, have been confirmed^{3-4, 6}. In the case of muscle, compounds called myokines are released in response to voluntary contraction. Myokines are cytokines, yet are derived specifically from muscle. These myokines give instructions to the body about how to function and hold the key to controlling chronic inflammation. The most important myokine related to muscle and inflammation is IL-6. When muscle contracts, IL-6 is released.

IL-6 is a well known cytokine and has long been thought to be inflammatory in nature as part of what is known as the inflammatory triad; TNF-alpha, IL-1, and IL-6. However, like people, IL-6 seems to behave differently depending on its origin, amount, and other cytokines around with it. When released from muscle and in high concentrations without TNF-alpha and IL-1, IL-6 is anti-inflammatory^{10, 12}. In fact, IL-6 acts to reduce the amount of TNF-alpha and IL-1 in circulation by increasing the cytokine inhibitors IL-1 receptor antagonist (IL-1ra) and soluble TNF receptors (sTNFR)^{5,7,8}. IL-1ra antagonizes the IL-1 receptor decreasing IL-1 effects while sTNFR binds up TNF-alpha before it can react at its target cells. At the same time, IL-6 triggers the release of the major anti-inflammatory cytokine IL-10^{7, 8}.

It appears exercise induced IL-6 has unique action as opposed to TNF-alpha mediated release of IL-6¹⁰. Exercise causes a huge rise in IL-6 far and above TNF-alpha levels. This is in sharp contrast to infection or sepsis which shows an exponential rise in both. It may be the ratio of IL-6 to TNF-alpha that is the real concern in regards to chronic inflammation. Epidemiological studies on TNF alpha and IL-6 genetic polymorphisms support this showing those with the highest TNF alpha and lowest IL-6 levels have the greatest risk of diabetes³⁷. Other researchers support TNF alpha as the real inflammatory culprit¹⁰. They speculate IL-6 levels may be a marker of whole body TNF-alpha levels and could be acting in direct opposition to the more inflammatory cytokines. The IL-6 effect implicates exercise as a first line defense against inflammation and may explain the “counter-intuitive” findings on the benefit of resistance training in highly inflammatory diseases like rheumatoid arthritis²⁶.

IL-6- The exercise factor

For sometime, science has been searching for a molecule that could account for the acute metabolic effects of exercise. Exercise reduces “all cause mortality” due to its effects on the leading killers; heart disease, diabetes, and cancer³⁵⁻³⁶. IL-6 is also beginning to be shown to be protective against diseases like diabetes^{12, 14, 16}. These same diseases have strong links to inflammation which is now suspected as a major underlying cause. It has long been thought that exercises impact on weight loss was the reason behind this. However, IL-6 also plays a role as a mediating factor in exercise’s effects on fuel metabolism^{1, 3, 4, 6, 15}. The broad effects IL-6 has on inflammatory cytokines, fuel metabolism, plus its ability to “talk” to the brain, liver, and adipose tissue, has some researchers thinking it is the best candidate for the elusive exercise factor⁶.

As muscle contracts, the genes controlling IL-6 production are turned on. The degree of IL-6 released from muscle is directly proportional to the amount of muscle being contracted; the more

muscle used, the greater the response^{5, 7, 38, 40}. IL-6 also shows a tight relationship to muscle glycogen and exercise intensity. When muscle sugar stores begin to decrease, an intensity threshold is breached and much larger amounts are released⁴⁰. Rising exercise intensity, full body muscle contraction, and muscle glycogen depletion are the major exercise elements enhancing IL-6 release from muscle^{11-12, 38}. These factors together can induce an increase of plasma IL-6 that is twenty to 100 fold over resting levels^{5, 41}. When at these levels, IL-6 begins to exert influence over the body relaying messages about the metabolic needs of the muscle. In this way, IL-6 acts more like a hormone than a cytokine; sending communications from muscle to adipose tissue, immune cells, and the liver. These messages instruct the body to burn fat, control glucose regulation, inhibit the production of the pro-inflammatory cytokines, and ultimately generate a fully anti-inflammatory effect through the release of IL-10⁸. IL-10 is a potent reducer of TNF-alpha and IL-1 in its own right¹⁰.

From the above scenario, it should be apparent that the ability to harness IL-6 through exercise can have a significant effect on not only inflammation, but whole body fuel usage, and tissue repair. This process is far different than the usual chronic inflammatory scenario. A situation of chronic inflammation is one where TNF alpha is elevated along with IL-6 and IL-1. Exercise induced, muscle derived IL-6 shifts the balance causing a reduction in TNF-alpha and IL-1 with a simultaneous rise in IL-10.

Other effects of exercise induced IL-6

In addition to its more direct effect, exercise induced IL-6 has other secondary effects that account for increased benefits. 11-beta Hydroxysteroid dehydrogenase type 1 (11-beta HSD 1) is an enzyme that should be on the radar of physicians. It is responsible for the conversion of cortisone into active cortisol. This cortisol/cortisone ratio is important in keeping the detrimental effects of cortisol at bay by deactivating it to cortisone. This enzyme is present in visceral adipose and is overly active in the overweight and obese¹³. This is an important revelation as it points to visceral adipose tissue as a new site of cortisol production. TNF-alpha and IL-1 beta are both shown to upregulate 11-beta HSD 1 and contribute to total glucocorticoid production¹³. IL-6 is a potent inhibitor of both TNF-alpha and IL-1 beta, and the largest amounts are released through exercise. Intense exercise potentiates these effects by increasing sympathetic stimulation of alpha 2 receptors as well as ACTH; all of which have independent effects in suppressing HSD-1 activity. The ability to blunt the HSD 1 enzyme is beneficial in controlling obesity and diabetes and intense exercise may be the best way to effect these changes.

In addition to the cytokine effects, IL-6 crosses over into hormonal action and allows the muscle to “talk to the adipose tissue”⁴. In response to exercise, IL-6 from muscle acts at distant sites including the liver and adipose tissue. Its major action at these sites is to release energy substrate to fuel continued movement. IL-6 is a potent stimulator of adipose tissue fatty acid oxidation and is a major factor in liver glycogenolysis^{1, 4}. While the mechanism for this action has not yet been fully elucidated, studies have confirmed IL-6 has direct effects on the expression of AMP-kinase and hormone sensitive lipase; two chief fuel regulating enzyme in human tissue^{15, 47-48}.

Finally, IL-6 has the ability to cross the blood brain barrier having direct effects on the brain. As a matter of fact the brain itself produces IL-6 in response to exercise as well. This sparks

curiosity as to what brain IL-6 is doing? Animal studies show that IL-6 is having a direct and important effect on the brain. These studies show IL-6 playing a role in appetite regulation, fuel regulation, and body composition ¹⁶.

Exercise approaches to inflammation

IL-6's release from muscles cells is not a nervous system phenomenon and is not based on muscle injury. It seems the impetus for IL-6 release is mechanical ^{6, 40}. In other words, just the act of movement is all that is required. However, there are ways to amplify the IL-6 production during exercise. The science of exercise metabolism now goes far beyond simple calories. The ability to harness the far ranging hormonal and cytokine effects of exercise can be accomplished through the use of short duration high intensity exercise techniques used in athletic populations for decades. Although the term "high-intensity" has the tendency to cause reservation, these tools and techniques can be adapted to use in even the least fit and most inflamed populations ¹⁷⁻²⁶.

Before discussing the techniques in this approach to exercise, it is important to define why short intense exercise is best. The damage associated with chronic inflammation is compounded by a lack of offsetting growth factors. The body produces these growth factors in response to intense exercise. Testosterone and especially growth hormone are known to be factors linked closely with intensity. The word intense as we are describing here means exercise that is glycogen depleting, i.e., significantly reduces the bodies muscle and liver sugar stores. Only two types of exercise are able to produce these effects long duration exercise lasting hours or short intense sprint type exercise. There are obvious constraints to prescribing hour long exercise sessions as lack of time is the number one reason cited for lack of exercise participation making short intense exercise not only more beneficial, but more realistic. In addition, the overall hormonal response to long duration exercise is counterproductive as it raises cortisol levels above the body's ability to compensate with growth promoters ²⁷⁻³⁴.

High intensity exercise using short burst of all out effort significantly alters glycogen stores, and can be easily managed through the use of intervals; periods of all out effort interspersed with rest. This type of activity is manageable by those considered most frail in terms of exercise prescription including COPD ¹⁹⁻²⁰, post bypass patients ²², congestive heart failure ²³, and even heart transplant patients ¹⁸. This type of anaerobic stimulus more realistically mimics real world challenge and allows for self paced exercise that is safe, tolerable, and more beneficial for many heart and lung patients ¹⁷⁻²⁵. Cardiac patients also have less risk with this type of activity as it has more favorable effects on ST segment changes and heart rate variability ^{21, 24-25}.

This type of exercise also makes sense because it creates a hormonal environment that produces sustained fat burning as well as muscle growth ⁴²⁻⁴⁴. The amount of glycogen reduction is directly correlated to IL-6 release and high intensity exercise is shown to increase IL-6 and catecholamines together ^{5-6, 11, 49}. Catecholamines have their own independent effect in lowering TNF alpha and IL-1, synergistically enhancing IL-6. Combining these known effects with techniques that can deliver the same benefit in less time presents the opportunity to supply these anti-inflammatory effects in short time periods ^{45, 46}.

The anti-inflammatory workout.

The most efficient way to generate an ample IL-6 response to exercise is to combine resistance training and aerobic exercise in one workout. This allows the body to quickly dip into anaerobic metabolism where glycogen stores are rapidly depleted to sustain energy. Relying strictly on aerobic metabolism makes significant glycogen reduction unlikely in the time periods most are willing to exercise. Combination workouts also allow the body to efficiently switch from aerobic to anaerobic metabolism and back again. This is a useful metabolic skill considering cardiovascular events can be induced by unexpected anaerobic challenges the body is not prepared to handle. Examples would be shoveling the first winter snow or running to catch an airplane. It is prudent to train this energy system, and it accomplishes significant risk reduction

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The types of exercises used also should move away from more conventional exercises. Exercises that involve large muscles and combine multiple joints stimulate a large amount of muscle contraction and supply a better stimulus for IL-6 release⁶. Hybrid exercises that combine two or more traditional types of exercise in one movement are able to stimulate large amounts of muscle, and cut down on time in the gym. An example of this type of movement would be combining a squat exercise with a shoulder press. Rather than performing the exercises separately, they are merged together so that the completion of the squat is immediately followed by the press in one single movement. This same principle can be used to create a whole range of exercises that are more functional, less monotonous, and more efficient than traditional training methods.

Other useful tools to incorporate into the workout include short rest periods as well as metabolic and mechanical failure. While the failure component is not necessary to induce IL-6 release, it will ensure a large IL-6 surge. The ability to maintain exercise and the onset of a muscle “burn” is a good indication the muscle sugar supply is being taxed. The rest periods should be taken when needed with exercise being resumed as quickly as possible. The ability to speak is a good indication of exertion and usually corresponds to 85% of one’s V02 max⁵⁰. A person should push until they have to rest and then rest until they can push again. Using heart rate measures coupled to exertion scores based on the ability to speak, exercise participants can create a safe workout that delivers a large dose of anti-inflammatory mediators.

The easiest way to incorporate the short rest periods and failure concept is to use supersets and hybrid movements. A superset consists of two exercises done back to back without rest. A short cycle can be set up so that three to four exercises are done back to back in succession and repeated until the participant must stop or reaches his or her limit. Once that occurs, the participant can rest until they are able to continue again, using the ability to talk as a guide. The use of a stopwatch allows the exerciser to time themselves for 10, 20, or 30 minutes. This creates an efficient workout that induces a large IL-6 response and also excels at increased fat burning and optimal hormone metabolism.

Final comments

Inflammation is one of the body's natural protective mechanisms, but when it becomes chronic it can turn destructive. Movement has historically kept inflammation in check through its anti-inflammatory mechanisms. As human movement has decreased, chronic inflammation has become rampant and contributes to all the major killers. The power of intense exercise to combat inflammation has been illustrated. A fast moving workout using full body movements, minimizing rest, and focusing on glycogen depletion can insure adequate anti-inflammatory effects. This same style workout can be tailored to the fitness level of the participants through the use of a self controlled interval format. Heart rate monitoring and perceived exertion measures based on the ability to speak allow for a safe and effective workout in even the frailest. Exercise is an underutilized healing modality despite its known benefits. With an understanding of its anti-inflammatory effects, exercise can now be seen as a useful adjunct or first line therapy in all diseases of chronic inflammation

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