

## Interleukin-6: Exercise's Fat-burning Hormone

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An unlikely relationship has recently been discovered and is making headlines in medical journals. Inflammation and obesity are rarely spoken of in the same sentence. Yet, unbeknownst to even the most vigilant scientist, fat cells have been using the information network of the inflammatory system to secretly conduct sabotage against our bodies.

Inflammation refers to the body's response to damage, infection or anything recognized as being irritating or foreign (poison ivy, a splinter, transplanted organs or even one's own organs if they suffer from an autoimmune disorder like lupus or rheumatoid arthritis). Damaged cells release chemical signals that attract white blood cells, which either attack the damaged or foreign cells directly or label them for removal by filtering organs (thymus, spleen, etc.). Many of the chemical messengers are components of a class of molecules called cytokines. Among the many cytokines is one that has been the subject of a great deal of research called interleukin-6 (IL-6).

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### Vital to Overall Health

IL-6 is one of the first cytokines of the inflammatory signal cascade, stimulating the release of further cytokines. It's commonly been referred to as a pro-inflammatory cytokine as it's one of the earliest responders to an inflammatory situation. As is often the case, as scientists learn more about IL-6, they discover how little they actually know.

In addition to promoting inflammation in certain settings, IL-6 also has anti-inflammatory actions. The difference often lies in the tissues releasing or responding to IL-6 and the time course of the inflammatory event. For example, when the body first recognizes an infection, IL-6 amplifies the immune response to the offending agent (bacteria, bullet, etc.). This was believed to be the sole physiologic effect of IL-6 until later research determined that various cells respond to the cytokine (IL-6) in different ways depending on the type of tissue involved and even the metabolic state. IL-6 also stimulates the release of anti-inflammatory components, such as IL-1Ra.

It's not overly surprising that the body maintains a balance in a system as vital to overall health as the immune/inflammatory system. If the immune system is suppressed (as may happen with overtraining, extreme weight loss, corticosteroids such as prednisone, cancer, AIDS or age) then the body becomes more susceptible to many diseases and infections, including viral infections, sepsis and certain cancers.

When the immune system is overly active, the body isn't necessarily hyper-protected because it's not like putting on extra layers of clothes. Instead, the immune system may become an angry mob and look for something else to attack, often the host itself (your body). This is what happens in the case of autoimmune diseases, many of which are familiar even if they're not understood as being examples of the body turning against itself. Several forms of arthritis are autoimmune disorders—rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, as well as type 1 diabetes, multiple sclerosis and certain thyroid disorders.

## Of Most Interest to Guys Who Work Out

Clearly, the immune system defies an easy understanding, even when it's functioning properly. However, scientists are scrutinizing the immune system with great interest in the hopes of developing therapies to treat many of the diseases afflicting the world's population. There's hope that the cure for several diseases may be managed by stimulating a person's own body to correct or eradicate cancerous tumors, viral infections such as hepatitis or HIV, autoimmune disorders and of most interest to those trying to get fit—obesity.

Since their discovery, fat cells have been considered passive storage sites, existing merely to hold extra energy to allow our ancestors to withstand periods of famine. Yet clandestinely, fat cells have been communicating via a system of hormones and chemical signals to aid in the control or balance of whole body energy. Many great discoveries have been made in the last 25 years dealing with adipocytes (fat cells) as an endocrine organ. The most simple to understand have been the endocrine-like effects of hormones such as leptin. Leptin travels to the brain and signals to the body the amount of stored fat. When leptin is high due to a large fat mass, the brain responds by lowering appetite and increasing metabolism. When leptin drops due to low fat mass, the brain increases the appetite and lowers metabolism. This stimulates the low-leptin individual to eat more and preserve energy. This discovery excited scientists who hoped that injecting obese people with leptin would help them to lose weight. Unfortunately, it didn't, as most obese Americans aren't deficient in leptin, but rather resist the hormonal signal.

With the dawn of the new century, several intriguing studies have been published, describing other messengers used by the fat cells to communicate with distant organs in the body (brain), nearby tissues and cells (other fat cells) and even self-regulation (same cell). These processes are referred to as endocrine, paracrine and autocrine functions. They all utilize chemical messengers to change the metabolism; the primary difference is the target cell, whether it be far, near or even the cell talking to itself. Many of the chemical messengers related to fat cell function have been implicated in a variety of diseases, including type 2 diabetes, cardiovascular disease and obesity. According to the published literature, IL-6 appears to hold a prominent position in these relationships.

### A Potent Messenger

The earliest data regarding cytokines (IL-6 specifically) and body fat were confusing and often contradictory. Researchers noted that relatively high IL-6 levels in the blood, a sign of chronic, low-level inflammation, is associated with insulin resistance, obesity and the development of type 2 diabetes. Further, IL-6 directly stimulates the production of C-reactive protein (CRP), a marker associated with the development of cardiovascular disease and type 2 diabetes.

Yet, despite all this evidence showing elevated blood levels of IL-6 are associated with obesity, insulin resistance, type 2 diabetes and cardiovascular disease, other studies strongly support a lipolytic (fat reducing) effect of IL-6 on fat cells and whole body fat. Early animal studies demonstrated that mice injected with IL-6 had higher free fatty acid blood levels, indicative of lipolysis (fat release). Mice born without IL-6 develop obesity later in life, but this is corrected with IL-6 treatment, suggesting that IL-6 plays a role in energy balance for rodents.

Studies using fat cells from humans demonstrated that IL-6 induces lipolysis by 26 percent to 79 percent; leptin production was increased when cortisol was present; and the effect of insulin on the enzyme lipoprotein lipase, which is necessary to transport fat from the blood into the fat cell, was reduced. When infused (injected slowly via an IV) into healthy adults, IL-6 increased lipolysis by 50 percent and increased cortisol and GH.

Though the evidence isn't considered conclusive by scientists, there's strong evidence suggesting that IL-6 may be one of the more potent messengers signaling for fat loss on an autocrine or paracrine level (affecting the same or nearby cells). The level of impact on fat loss or gain may not be as potent as insulin or norepinephrine (a nerve signal similar to adrenaline), but it's significant.

## Pushing the Inflammatory Response

IL-6 is present in fat tissue in much higher amounts than is found in the blood. In fact, IL-6 concentrations in fat tissue exceed 100 times the blood level. The signaling mechanism for producing and secreting IL-6 is complex. However, some key players are present that help explain the interrelationship between inflammation and lipolysis.

Norepinephrine, the excitatory nerve signal that turns on fat loss with products like ephedrine and caffeine, stimulates the inflammatory cascade in fat cells, including IL-6 and tumor necrosis factor alpha (TNF). Interestingly, the amount of IL-6 produced is greater in larger fat cells, which are seen in disease states and obesity. In the presence of the high local concentrations of IL-6, fat cells release stored fat as free fatty acids with greater amounts coming from larger fat cells.

Other reactions take place in the fat cells, including changes that make the fat cells resistant to insulin. By blocking the fat cell's response to insulin, less fat is taken into storage from the blood, protecting the body from accumulating too much fat. Unfortunately, this only happens if the diet is controlled. Daily buffets and nightly tubs of ice cream force the fat cells to push the inflammatory response into overdrive. As a consequence, high levels of free fatty acids and IL-6 enter the bloodstream. From the subcutaneous fat (the kind you can pinch), the excess IL-6 and free fatty acids enter the circulating blood and likely account for much of the basal IL-6 seen at rest. However, the real problem comes from the visceral fat (the fat inside your abdominal cavity and that lines the organs of your gut). Visceral fat has a much higher rate of production of IL-6 and is more fibrovascular. This is important because it's been determined that as much as 90 percent of fat-associated IL-6 actually comes from the fibrous tissues and blood vessels that support the structure. The obese also seem to collect inflammatory cells within fat, which further stimulate and generate inflammatory cytokines. Making the matter worse is the fact that visceral fat drains directly into the liver, rather than being diluted in the circulating bloodstream.

The liver is a critical organ. It plays a vital role in controlling the amount of sugar and fat circulating in the body. It's also the site of production for many important proteins. When high levels of free fatty acids enter the portal circulation (the primary bloodstream for the liver), the liver packages them up into triglycerides and sends them into the circulating bloodstream to be taken up by fat cells or working tissue (like muscle). However, when present in excess, triglycerides can build up in the bloodstream and may cause plaques, which can block blood flow and lead to heart attacks or strokes.

The liver also gets assaulted by high levels of IL-6, which can induce inflammation in the liver, causing cellular damage or scarring, and damage the liver's ability to respond to insulin. When the liver becomes insulin resistant, it fails to properly control the body's supply of sugar. Sensing a need for more sugar, it turns off sugar storage, breaks down amino acids to create new sugar and pumps out the newly created sugar into the bloodstream, which already has sufficient or high sugar levels. Normally, this process is turned off by the insulin surge that accompanies meals, but as the liver no longer responds properly to insulin, muscle is robbed of amino acids to feed the sugar-producing process and new sugar continues to enter the bloodstream, even as a meal is being consumed. Correcting the insulin-resistant state of the liver is believed to be one mechanism for the success of metformin in reducing body fat.

## Other Affected Tissues

Other tissues besides fat and the liver are affected by IL-6 that relate to body fat and chronic diseases. Skeletal muscle is a site of IL-6 production, and the amount of IL-6 generated is greatly increased by exercise. Cell studies and biopsies from subjects infused with IL-6 demonstrate that exercise can increase skeletal muscle production of IL-6 by 100 times. Skeletal muscle IL-6 production is stimulated by the muscle contracting and the influx of calcium that rushes into the muscle cell. The degree of IL-6 production appears to be related to the intensity of the exercise, as rowers (intense

group) experience a two-fold increase in blood IL-6 within six minutes of exercise, whereas long-distance runners don't show an IL-6 peak until after exercise ends. Also, it's been shown that IL-6 peaks higher when glycogen is low, possibly suggesting one pathway for the greater fat loss seen in low-carbohydrate diets.

IL-6 not only activates lipolysis in exercising muscle, but also increases the rate of fat oxidation (burning fat for calories). Contrary to other tissues, IL-6 doesn't interfere with the insulin signal, allowing exercised muscle to take in sugar and amino acids from the blood. Other tissues become insulin resistant when exposed to IL-6 (this will be discussed later). IL-6 may also act as an anti-inflammatory signal in exercised muscle. Another cytokine, called tumor necrosis factor alpha (TNF), causes insulin resistance in many tissues, including skeletal muscle. In the presence of exercise-elevated IL-6, TNF production is markedly suppressed in that tissue. This is important, because IL-6 and TNF production are both stimulated by epinephrine (adrenalin), which is present in high concentrations during exercise. Without the anti-inflammatory effect of IL-6, skeletal muscle would become insulin resistant following exercise, interfering with glycogen replenishment, amino acid uptake and repair. The brain is another important site of IL-6 action. Though the experiment hasn't been attempted on humans, it's been shown in animals that infusing IL-6 into the fluid surrounding the brain reduces appetite and leads to weight loss. It's likely that this is also a mechanism of action in humans, as obese individuals have lower levels of IL-6 in the fluid surrounding the brain and spinal cord.

### Reducing or Controlling IL-6

So, even though there's a lot of evidence that IL-6 increases lipolysis and promotes fat burning in skeletal muscle, two real questions remain— is it good for you and how does one control it?

Clearly, high amounts of IL-6 aren't good in the bloodstream or the liver. Yet, when IL-6 acts on the fat cells, it increases the amount of fat released; IL-6 protects muscles from inflammation, preserves insulin function and increases fat burning; and IL-6 suppresses the appetite and increases the metabolism in certain centers of the brain. The second question— how one controls it— becomes more relevant.

Reducing systemic IL-6 is crucial to long-term health, as it's associated with disease states that decrease lifespan and quality of life (diabetes, cardiovascular disease, insulin resistance). Also, remember that IL-6 concentrations are markedly higher around muscle and fat, so a relative drop in blood IL-6 that might promote health isn't likely to impair fat loss.

IL-6 levels have been noted to decrease with weight loss in the obese, through diet and exercise (though not so much from diet alone), in athletic populations and when fish oil replaces carbohydrates in the diet. A carbohydrate-restricted diet reduces CRP and TNF, two other components of inflammation, but IL-6 levels won't change through carbohydrate restriction alone.

Several medications have been suggested to treat a state of chronic inflammation (elevated inflammatory cytokines), including: thiazolidinediones (TZD), statins, aspirin, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers. Recent headlines have promoted the effectiveness of one TZD called Avandia in not only treating, but also preventing type 2 diabetes. Combining this news with the reports of Avandia being able to lower adipokines and reduce bodyweight makes it a promising drug to consider.

Statins, particularly pravastatin (Pravachol), are being investigated for their ability to reduce cytokine-related ills. Reducing morbidity and mortality by controlling inflammation and the maladies associated with fat-related cytokines is

generating a tremendous amount of clinical interest at this time.

For those interested in evaluating their risks relating to chronic inflammation, a simple lab test called C-reactive protein can be ordered. If elevated, it may indicate a need to exercise more (intense weight training rather than low-intensity cardio), lose fat, replace carbohydrates with fish oil and discuss the previously mentioned medications with your personal physician. While IL-6 holds a very important role in regulating fat, it needs to be controlled lest it causes damage that may shorten lives or make them less enjoyable.

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