

Uncoupling Proteins and Fat Loss: Misplaced Hopes?

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It has long been known that certain animals are able to regulate body temperature and alter their metabolism through the action of a bizarre type of fat called brown adipose tissue (BAT). This appears to be mediated in large part by a specific protein located in the mitochondria of BAT called uncoupling protein-1 (UCP-1). UCP-1 acts by making the mitochondria "leaky," allowing protons (electrically charged hydrogen atoms) to escape from the interior of the mitochondria. Mitochondria are small organelles present in most cells, consisting of an inner chamber surrounded by an outer chamber. Mitochondria are responsible for generating ATP (the energy molecule) and resynthesizing phosphocreatine, the high-energy form of creatine.

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ATP, the energy molecule, is generated in the mitochondria by a process known as oxidative respiration, an oxygen-requiring chain of chemical reactions that break down fats and metabolites of sugars or amino acids into carbon dioxide and water. Oxidative respiration is driven by enzymes and electro-chemical differences between the inner and outer chambers of the mitochondria. The electro-chemical difference is called the proton gradient, as it's determined by the level of positively charged hydrogen ions, or protons. Though the process is complex, knowing the details is not necessary to appreciate the function of the mitochondria. So long as the chain of events is undisturbed, calories are burned and ATP is generated.

When the Chain is Disturbed

When the chemical chain reaction is disturbed, the mitochondria become less efficient and more calories are burned to generate the same amount of ATP. In disease states or in certain cases of poisoning, this disturbance can be severe, even deadly. However, physicians and scientists have long been aware of the potential for disturbing the mitochondrial process only slightly in order to treat obesity.

Most hardcore bodybuilders have heard of, if not experimented with, dinitrophenol (DNP); a chemical used in certain manufacturing processes. Physicians used DNP to treat obesity during the first half of this century, but ceased the practice as cataracts and other problems arose. During the Second World War, factory workers in a munitions plant (bombs) became ill or died due to exposure to DNP dust. More recently, a bodybuilder's death due to DNP made national news. DNP is an extremely potent uncoupler that produces drastic fat loss and increases body temperature (a side effect of mitochondrial uncoupling), but carries an unacceptably high risk of injury or death. Long-term use of DNP increases the risk for cellular damage and degenerative diseases, as it creates high levels of free radicals. Free radicals damage proteins and DNA, interfering with cellular function and increasing the risk of certain cancers.

The pursuit of effective, but safe, uncouplers continues; thus far, it has been without success. An uncoupler introduced briefly into the dietary supplement market, usnic acid, was pulled from the market by the FDA after several cases of liver failure were reported.

Pharmaceutical companies have recently tried a different attack at the uncoupling mystery. Rather than attempting to create a chemical uncoupler, efforts at modifying natural uncoupling mechanisms began. Recall that UCP-1 is responsible for maintaining body temperature in the brown fat of small animals and accounts for as much as 20 percent

of energy expenditure (calorie burning). Initially, this was of little value, as adult humans do not have appreciable amounts of brown fat and UCP-1 is not found elsewhere in the body. However, it was discovered that similar uncoupling proteins are found throughout the body. These novel UCPs do not behave exactly like UCP-1, but due to the close chemical pattern, they held promise as possible metabolic modifiers in humans. There are at least five different forms of UCPs, with different distributions. The two forms that are clinically important are UCP-2 and UCP-3.

UCP-3: No Silver Bullet

UCP-2 has received a great deal of attention due to its presence throughout the body. It's present in many important tissues, including brain, pancreas, liver and adipose. UCP-3 is the more relevant form for the purposes of weight loss. It's present primarily in the skeletal muscle, the principle target tissue for stimulating calorie burning.

Scientists cloned UCP-3 and inserted the gene into yeast, and discovered that high levels of UCP-3 increased a certain category of respiration (energy utilization). This early finding supported the hypothesis that UCP-3 has a metabolic function in the human. Moving forward, scientists then inserted the gene into mice to study the effect of elevated levels of UCP-3 in animals. As would be expected, mice with greater UCP-3 levels exhibited an uncoupling effect.

Armed with this information and experiences, scientists fully expected to be able to manipulate UCP-3 levels in humans and thus have a new "silver bullet" in weight management and fat loss. Unfortunately, this has not proven to be the case. Evidence from human studies suggests that the uncoupling process has multiple control mechanisms and does not affect metabolism under normal physiologic conditions. However, this may not be the final word on uncoupling.

The research surrounding the uncoupling process in humans is complex and suffers from a lack of standardization. Examining some of the studies should show why it seems likely that manipulation of UCP-3 in humans is not likely to be a fruitful area of research in the near future.

Levels of UCP-3 are determined by a variety of methods, but nearly all of them are flawed. In part, this is due to the fact that proteins, like UCP-3, are regulated by a number of control mechanisms. UCP-3 is produced when DNA is stimulated to open up (it normally is folded upon itself like a ball of yarn). Next, the DNA pattern is used as a blueprint for a messenger string of nucleic acids (the NA in DNA) called mRNA. DNA is not used for direct production of proteins. The mRNA links amino acids together in a specific order to create specific proteins. The newly formed protein then enters the place in the cell where it functions under the influence of other factors, such as substrate supply, pH, co-enzymes, inhibitors, etc.

One important point to consider is that the levels of DNA, mRNA and protein are not always closely related. In addition, the amount of protein formed does not relate to the level of activity. As an example, the UCP-3 gene (DNA) is present in nearly all people. The level of mRNA produced is variable and may increase or decrease for reasons not related to the metabolic rate of the cell. Further, the mRNA may or may not be used to produce UCP-3 protein. Regardless of how much UCP-3 is produced, the level of activity can be vastly different from what would be expected based upon UCP-3 levels.

What the Science Shows

This is confusing, which is the point. It would be like trying to guess whether a person might purchase a DVD player. Is it easiest to guess based upon the person's occupation, income, or amount of money in his wallet? In fact, the best way to determine whether the purchase is made is to watch and see if the person actually buys. It matters little how much the person makes or how much he has in his pocket. It only matters whether or not he actually buys the item- the activity.

Herein lies the problem with human UCP-3 research. Most research has measured UCP-3 mRNA levels to determine the

relationship between UCP-3 and metabolism; much like asking people how much money they have, then trying to guess what they will buy. These studies show little relationship between the amount of UCP-3 mRNA and calorie burning. Based upon these studies, the only conclusion that could be drawn is that UCP-3 has little to do with the metabolic rate.

A more relevant research design was used in a recently published study. European scientists, including the well-known creatine investigators Greenhaff and Hultman, evaluated the relationship of UCP-3 levels and activity on phosphocreatine resynthesis. Remember that the role of creatine is to shuttle high-energy phosphate from the mitochondria to the cell interior where it restores ATP. It does this by traveling into the mitochondria as creatine, where an enzyme transfers a high-energy phosphate from ATP (which is in high concentration inside the mitochondria) to creatine, creating phosphocreatine. It has been previously established that UCP-3 levels increase when subjects consume a high-fat diet, as compared to a low-fat diet.

Nine healthy adult male subjects consumed a low-fat diet for seven days, and then they performed a set of intense leg extensions while wearing a tourniquet around the upper thigh. The tourniquet blocked blood flow, preventing any oxygen from reaching the exercised muscle, depleting the intracellular oxygen and essentially stopping ATP production through oxidative respiration. Muscle force was measured during the set and phosphocreatine resynthesis calculated after the tourniquet was released and blood flow was restored. The same subjects returned after consuming a high-fat diet for seven days, which increased UCP-3 protein levels 44 percent, and the test was repeated.

The investigators found no difference between the low-fat and high-fat periods in muscle performance or phosphocreatine resynthesis. This study clearly shows that under physiological conditions, an increase of 44 percent in UCP-3 protein does not have an uncoupling effect on human skeletal muscle. How is this reconciled with the earlier studies showing such promise in the yeast and mice? In part, it's a matter of degree. UCP-3 appears to be able to affect mitochondrial function when increased to supraphysiological levels. The UCP-3 concentration in the yeast was 700 percent higher than human levels. UCP-1 levels in the brown adipose tissue of rats are 200 to 700 times higher than the UCP-3 levels in human skeletal muscle. It seems clear that the function of UCP-3 in humans is other than uncoupling, though under altered states (chemical poisoning, infection or disease) it may affect energy expenditure via an uncoupling effect.

Drawing Conclusions

It remains to be discovered what the true function of uncoupling proteins are in humans, though it appears that under physiological conditions, they do not have a role in regulating metabolism. It has been proposed that UCP-2 and UCP-3 have a protective role, removing non-esterified fatty acids (fats that are not processed correctly to be burned as calories) from the mitochondria. This is important, as non-esterified fatty acids can become damaging free radicals. UCP-2 and UCP-3 also appear to remove reactive oxygen species, extremely potent free radicals that can damage DNA or cellular proteins. There are several observations supporting this theory. As UCP-3 levels decrease with age, this area of research may be of greater significance in anti-aging and disease prevention than in fat loss.

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