

Crank up the heat: Uncoupling Proteins

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Over the last few years it has been increasing evident that low carb diets are more effective for weight loss than low fat diets^{1, 9, 10, 11}. In addition to losing more weight, low carb diets also seem to improve lipid profiles. One study reported that an Atkins-style diet approach, which included a vitamin and nutritional supplements lost more weight than a low fat diet. Along with losing an average of 26 pounds, dieters assigned to the low-carbohydrate plan lost more body fat, and lowered their triglyceride levels and raised their HDL, or good cholesterol, more than the low-fat dieters. The low-fat dieters lost an average of 14 pounds². Many nutritionists once thought that high fat/high protein diets were more effective for weight loss than low fat diets simply due to reduced caloric intake; however low-carbohydrate diets do more than just curve the appetite but also turn on fat burning genes.

Over the last few years it has been increasing evident that low carb diets are more effective for weight loss than low fat diets^{1, 9, 10, 11}. In addition to losing more weight, low carb diets also seem to improve lipid profiles. One study reported that an Atkins-style diet approach, which included a vitamin and nutritional supplements lost more weight than a low fat diet. Along with losing an average of 26 pounds, dieters assigned to the low-carbohydrate plan lost more body fat, and lowered their triglyceride levels and raised their HDL, or good cholesterol, more than the low-fat dieters. The low-fat dieters lost an average of 14 pounds². Many nutritionists once thought that high fat/high protein diets were more effective for weight loss than low fat diets simply due to reduced caloric intake; however low-carbohydrate diets do more than just curve the appetite but also turn on fat burning genes.

High Protein/High Fat Diets Turn on Fat Burning Genes.

Several animal and human studies indicate that dietary fats increase the expression of genes regulating fat metabolism in skeletal muscle^{6, 7}. Plasma fatty acids are increased after a short-term high fat diet and also increase the expression of several key genes associated with fatty acid metabolism³. For example, one study investigated low and high fat diets and changes in enzymes that control fat metabolism in endurance trained men. Irrespective of training, beta-hydroxyacyl-CoA-dehydrogenase activity (β -oxidation enzyme controlling fat metabolism) in the thigh muscle was significantly increased by an average of 25% after adaptation to a fat-rich diet and was unchanged after adaptation to a carbohydrate-rich diet⁴.

Another study reported that in athletes in as little as 5 days on a high fat, high protein diet during a 20-min exercise bout, fat oxidation was increased almost 2-fold greater after 5 days of the high fat diet than after the high carbohydrate diet; in conjunction there were significant increases in the fat oxidation enzymes in skeletal muscle after the high fat diet⁷.

Catecholamines Increase Brown Adipose Tissue

Adipose tissue is divided into two types: white and brown adipose tissue (BAT). Extensive work over the last 30 years, principally on rodents, has demonstrated the thermogenic function of BAT. BAT therefore contrasts with white adipose tissue, which stores energy. BAT contributes to an increased metabolism by the generation of heat, which contributes to increased basal metabolism. Brown adipose tissue is rich with sympathetic nerves and mitochondria, and is responsible for a major portion of the thermogenesis. In the resting state, about 90% of the oxygen consumption takes place in the mitochondria⁹.

Therefore, stimulating mitochondrial activity can increase thermogenesis. As promising as increasing brown adipose activity sounds, many researchers have given up on activating brown adipose tissue through the use of pharmacological drugs due to rapid loss of brown adipose tissue after birth in humans.

Beta 3-Adrenoceptor agonists are effective thermogenic anti-obesity agents in rodents. Their main sites of action are white and brown adipose tissue, and muscle. Beta 3-Adrenoceptor mRNA levels are lower in human than in rodent adipose tissue, and adult humans have little brown adipose tissue. A new study however challenges the notion that that brown adipose tissue is lost in adulthood, in fact the researcher's speculated we contain more brown fat than we previously thought however more research needs to be conducted¹².

Brown fat can be increased by chronic cold exposure but also beta-agonists which stimulate sympathetic activity. Brown adipose tissue is activated by increasing catecholamine levels; it has been shown that adults with pheochromocytomas (tumors of the adrenal gland which produce excess adrenaline) have more brown

adipose tissue than normal people¹⁵. Could long term use of supplements or drugs that increase thermogenesis increase brown adipose tissue? No one knows for sure but it may be possible. Activated BAT rapidly releases fatty acids and produces heat. This is achieved by the numerous mitochondria in brown adipocytes and a specific protein in the mitochondria called UCP (uncoupling protein), which activates respiration and diverts the free energy of oxidation to thermogenesis.

DNP: That's
Not Chicken I Smell Being Cooked...That's Me!!

Dan Duchaine introduced Dinitrophenol (DNP) a powerful stimulator of UCP several years ago as a powerful weight loss drug, but you would have to be crazy to take it. DNP, a benzene-based chemical, is nothing new and came to the attention of public health officials during World War I. DNP was used mainly in the manufacture of dynamite. Something unusual happened; the workers began building up considerable quantities of DNP in their bodies, both through skin contact and by inhaling the compound's vapors. At first the workers' symptoms were mild: sweating, light fever, increased appetite, heart palpitations, and insomnia. Then, as the days passed, the DNP levels in their bodies steadily increased along with more serious side effects as excess increases and body temperature and some people died. One of the more specific side effects of inhaling the compound was weight loss. After the war, physicians lost no time in prescribing it to dieters. In humans, it speeds up the metabolic rate until eventually the body burns itself up. Amazingly, DNP had the ability to stimulate metabolism by as much as 50% with noticeable increases in body temperature³⁵. The comparisons to the current drugs for increasing thermogenesis are a mere shadow of DNP at least in terms of thermogenesis. While the ephedrine/caffeine/aspirin stack has been shown to provide safe weight loss, it has only been shown to have an approximately a 3% increase in metabolic rate. Unfortunately DNP's therapeutic index was razor thin and it was not until thousands of people suffered irreversible harm (i.e. high dosages can cause blindness) that mainstream physicians realized that DNP risks outweighed its benefits and abandoned its use. Doctors reported that some patients on autopsy that used high dosages of DNP were literally "cooked to death." Researchers are still researching safe and effective ways of increasing UCP. There are several types of UCP's that can be increased safely by diet and thermogenics.

UCP-1: Works Great in Rats...Not so well
in Humans

UCP-1 is found

predominately in brown adipose tissue and is responsible for thermogenesis (production of heat). When UCP's are turned on there is an increase in heat production, metabolism, and resting oxygen consumption. Beta-adrenergic-receptor stimulation, due to pharmacological agents, has both acute and chronic effects on brown adipose tissue. UCP-1 activity increases within seconds of stimulation, while chronic stimulation over hours and days results in increased amounts of UCP-1 protein and increased activation of brown adipose tissue¹⁴. As exciting as the research was on rats, the research on stimulating UCP-1 seemed to flop in humans. Rodents have a greater capacity for thermogenesis than humans. They have more brown adipose tissue than humans; they also have more UCP-1 than humans which makes a specific UCP-1 drug unlikely to be effective for humans. UCP1 is believed to play an important role in thermogenesis in rodents but not in humans, in whom brown adipose tissue is limited.

UCP-3: The Muscle Uncoupling Protein

UCP-3, which has a 60% similarity to UCP1, is highly expressed in skeletal muscle and, to a lesser extent, in brown adipose tissue and heart¹⁸. UCP-3 is the only expressed in skeletal muscle which makes it of particular interest to increasing metabolism. It is important to recognize that the level of UCP1

protein is 200- to 700-fold greater than UCP3 protein levels in skeletal muscle or BAT¹⁹. Although UCP-3 is expressed at much lower levels than UCP-1, increasing UCP-3 may enhance thermogenesis.

Gene Manipulations of UCP-3

It has been demonstrated that certain people whom have defective UCP-3 gene expression have decreased fat oxidation¹³. Decreased fat oxidation has also been documented in UCP-3 deficient mice³⁶. In recent studies of skeletal muscle of mice that overexpress UCP-3, there was an increased capacity for fat oxidation³⁷. Mice overexpressing UCP-3 have lower body weights than normal mice²⁰. Additionally, mice that overexpress UCP-3 are not only leaner; they eat more than other mice and have less body-fat. Additionally, when obese, otherwise healthy, subjects were placed on a 900 Kcal diet for 6 months lost weight at very different rates. Researchers

were curious why there were differences in the amount of weight loss. Diet-sensitive subjects, who lost weight at a greater rate than diet-resistant subjects, had 25% higher UCP-3 expression levels than diet-resistant subjects²³. So now that you understand that increasing UCP-3 can enhance weight loss, let's examine how to increase UCP-3.

Tripping

Mice have Increased UCP-3 Activity

DNP was the first drug to stimulate UCP activity but others drugs do as well. MDMA or ecstasy is a drug that acts as both a stimulant and psychedelic, producing an energizing effect. I don't know if you have been to a rave but those people twirling glow sticks are usually sweating their ass off!! Side effects of ecstasy are a noticeable rise in body temperature, faster heartbeat, skin tingles, sudden sweating and dilated pupils. So why all the sweating and increased body temperature? A recent in mice examined how ecstasy affected UCP activation. Mice treated with ecstasy underwent rapid increases in rectal and muscle temperature. Ecstasy also caused intense sympathetic activation and increased UCP-3 activity in muscle which may partly explain the rapid increases in body temperature. In the second part of the study, the researchers administered ecstasy to UCP-3 deficient mice, UCP-3 deficient mice did not have any rise in bodycore temperature demonstrating UCP-3 role in stimulating metabolism²⁰. This demonstrates that large increases in sympathetic activity increase UCP-3 activity. Don't be a dumbass and start trying ecstasy to increase UCP-3. There are much safer ways!

Catecholamines

Increase UCP-3

Drugs that increase the activity of the central nervous system are a potential therapeutic pharmacological treatment for obesity. Two drugs which stimulate metabolism and have profound effects on increasing UCP-3 are thyroid and sympathetic agents such as beta agonists (drugs that stimulate catecholamines) ¹⁸. Treatment with β_2 -adrenergic agonists (Salbutamol, Formoterol) has been demonstrated to increase UCP-3 expression in muscle fibers³⁰. Both thyroid and catecholamines are potent stimulators of metabolism. A recent study found that having a low resting metabolic rate is predictive of obesity. Muscle accounts for 20% of the basal metabolic rate so increasing muscle metabolism enhances fat oxidation. A significant portion of the variation in metabolic rate between humans can be accounted for by differences in the amount of skeletal muscle energy expenditure, and further support for a probable role

of skeletal muscle in mediating thermogenesis comes from the demonstration that adrenaline infusion, which causes a 25% increase in whole body energy expenditure in humans^{14, 16}.

Caffeine and Growth Hormone Increases UCP-3 Activity

Resting metabolic rate can be increased by 30% by the sympathetic nervous system agents²⁷ and by about 15% by growth hormone²⁸.

Growth hormone has also been shown to increase UCP-3 in muscle which may be a part of GH's powerful effect on fat loss^{39, 40}. Any supplement that increases adrenaline should increase UCP-3 activity. UCP-3 activity varies between people; research has demonstrated that of all of these possible regulators of the expression of the UCP3 between people, only norepinephrine (a sympathetic catecholamine) could explain part of the variability between UCP-3 expression in subjects. Interestingly, norepinephrine urinary excretion also correlated with resting energy expenditure³⁴. It should be of no surprise that many of the fat loss supplements target fat loss by increasing norepinephrine levels. Basically, the higher your norepinephrine levels are, the higher your resting energy expenditure and UCP-3 activity will be. Caffeine is a potent stimulator of norepinephrine and increases fatty acid mobilization has also been shown to increase UCP-3 activity³⁸. I suspect the combination of caffeine with ephedrine and yohimbine would further increase UCP-3 activity as all increase norepinephrine levels but no research is available.

Olive Oil, Palm Oil, and Fish Oils: Potent Stimulators of UCP-3

UCP-3 is upregulated in situations where fatty acid availability is higher than its oxidation rates, as for example fasting, treatment with thyroid, high-fat/high protein diets, and intense exercise⁸. UCP's are activated much more effectively by palm oil, olive oil, and fish oils than by saturated fats. Instead of consuming saturated fats before a competition, you may be get leaner by consuming more fish oils and olive oils. Researchers conducted a study to determine what fats led to the greatest increase in UCP. The results were as follow: 1. Palmitic acid (palm oil) 2. Oleic acid (olive oil) 3. Eicosatrienoic acid (omega 3 fatty acid) 4. Linoleic acid (safflower and sunflower oils) 5. Arachidonic acids

(meat, eggs, dairy fats). Palm oil might be another consideration as palm oil can increase UCP-3 activity as well. It has been shown that palmitic acid or palm oil led to a 10% increase in oxygen consumption. Consistent with previous studies showing that palm oil not only increases resting oxygen consumption but the expression of the UCP3 gene is approximately doubled by palmitic acid concentrations²⁴.

Another potent stimulator of UCP-3 is olive oil. After the various types of fat, there was an up-regulating effect of olive oil on UCP-3 expression in muscle. The expression of the UCP3 mRNA in muscle was significantly higher after olive oil feeding than beef fats. Total-body oxygen consumption, an index of resting metabolic rate, was significantly higher in rats fed olive oil than other fats tested³³.

The results of the data suggest that palm oil, olive oil, and fish oils are better stimulators of UCP-3 production than saturated fats¹⁷. Thus, not all fats are equal and certain types of fats can enhance diet-induced UCP-3 production in muscle.

Blocking Fats Reduce UCP-3 Expression

Clinical data also demonstrate a strong correlation between the amount of circulating fatty acid concentrations and skeletal muscle UCP-3, suggesting fat intake stimulates UCP-3 expression²⁵. Mingrone and colleagues found a 35% reduction in UCP-3 protein levels in subjects having undergone gastric bypass surgery²². But since gastric bypass surgery minimizes stomach capacity and reduces dietary fat absorption, the drop in fat absorption likely lowered UCP-3 expression in muscle.

Additionally, Dr. Civaterese at Pennington Biomedical Research center has shown that glucose ingestion during exercise lowered UCP-3 expression and other genes involved in fatty acid metabolism²⁶. The reduced expression of lipid metabolism genes during glucose ingestion during exercise may have been due in part to suppressed lipolysis and a lowering of circulating fatty acids. The new over the counter "fat blocker" drug "Alli" will probably lead to a reduced expression of UCP-3 I suspect, but no research is available at this time.

Leucine: The Ultimate Diet Amino Acid?

Leucine is an essential, branched chain amino acid that not only as a building block for protein synthesis, but is also a potent activator of the mammalian target of rapamycin (mTOR), a potent activator of many functions including protein synthesis, cell growth, and metabolism. Branched chain amino acids, especially leucine, have been speculated to play a key role in regulating metabolism. For example, Donato et

al reported that leucine supplementation during caloric restriction results in more fat loss and improves protein synthesis in muscle³¹. Get ready for more exciting news on leucine and fat loss. It was recently shown that doubling leucine intake while on a high calories diet substantially reduced diet-induced weight gain and improved glucose and cholesterol metabolism in mice. The use of L-leucine supplementation also resulted from increased resting energy expenditure associated with increased UCP-3 protein expression in skeletal muscle and in brown and white adipose tissues³². So leucine not only increases protein synthesis but also reduces bodyfat by increasing UCP-3....can't get much better than that!! Leucine is the one supplement you can't do without before a competition.

Key
Points:

UCP-3 is increased by growth hormone, thyroid, catecholamines, and caffeine.

UCP-3 is stimulated more by olive oil, palm oil, and fish oil than saturated fats.

UCP-3 is reduced by high carbohydrates and fat blockers.

New research suggests that Leucine stimulates UCP-3 expression in muscle.

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