

UCP-3's Role In Enhancing Fat Oxidation

Contributed by Robbie Durand
Thursday, 12 February 2009

Over the last few years, it has been increasingly evident that low-carb diets are more effective for weight loss than low-fat diets.^{1, 9, 10, 11} In addition to added weight loss, 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, caused more weight loss 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 pounds.² 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 curb the appetite—they 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 metabolism.³ 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 in the thigh muscle was significantly increased by an average of 25 percent after adaptation to a fat-rich diet and was unchanged after adaptation to a carbohydrate-rich diet.⁴ Another study reported that in as little as five days, athletes on a high-fat, high-protein diet—during a 20-minute exercise bout—increased fat oxidation almost twofold over those on a high-carbohydrate diet; in conjunction, there were significant increases in the fat-oxidation enzymes in skeletal muscle after the high-fat diet.⁷

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 percent of the oxygen consumption takes place in the mitochondria.²⁹ 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 challenges the notion that that brown adipose tissue is lost in adulthood. The researchers speculated we contain more brown fat than we previously thought however more research needs to be conducted.¹² 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 people.¹⁵ 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 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 such as excess increases in body temperature and some people died as a result. 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 percent.³⁵ 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 percent increase in metabolic rate. Unfortunately DNP's therapeutic index was razor-thin and it was not until thousands of people suffered irreversible harm (high dosages can cause blindness) that mainstream physicians realized that DNP's risks outweighed its benefits and abandoned its use. Doctors reported that some patients (upon autopsy) who 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 UCPs 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 UCPs 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 tissue.¹⁴ 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.

UCP-3: The Muscle-Uncoupling Protein

UCP-3, which has a 60 percent similarity to UCP-1, is highly expressed in skeletal muscle and, to a lesser extent, in brown adipose tissue and heart.¹⁸ 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 UCP-1 protein is 200- to 700-fold greater than UCP-3 protein levels in skeletal muscle or BAT.¹⁹ 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 who have defective UCP-3 gene expression have decreased fat oxidation.¹³ Decreased fat oxidation has also been documented in UCP-3-deficient mice.³⁶ In recent studies of skeletal muscle of mice that overexpress UCP-3, there was an increased capacity for fat oxidation.³⁷ Mice overexpressing UCP-3 have lower bodyweights than normal mice.²⁰ 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 six months, people lost weight at very different rates. Researchers were curious why there were differences in the amount of weight lost. Diet-sensitive subjects, who lost weight at a greater rate than diet-resistant subjects, had 25 percent higher UCP-3 expression levels than diet-resistant subjects.²³ So, now that you understand that increasing UCP-3 can enhance weight loss, let's examine how to increase UCP-3.

Tripping Mice And 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 body temperature, demonstrating UCP-3's role in stimulating metabolism.²⁰ This demonstrates that large increases in sympathetic activity increase UCP-3 activity. Don't be a dumb ass 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 that 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 fibers.³⁰ 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 percent 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 supports the probable role of skeletal muscle in mediating thermogenesis.

Caffeine And Growth Hormone Increases UCP-3 Activity

Resting metabolic rate can be increased by 30 percent by the sympathetic nervous system agents²⁷ and by about 15 percent by growth hormone (GH).²⁸ GH 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 expenditure.³⁴ 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, which has also been shown to increase UCP-3 activity.³⁸ I suspect the combination of caffeine with ephedrine and yohimbine would also increase UCP-3 activity as well as 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 when fatty acid availability is higher than its oxidation rates—examples would be fasting, treatment for thyroid, high-fat/high-protein diets and intense exercise.⁸ UCPs 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 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 led to a 10 percent increase in oxygen consumption. The expression of the UCP-3 gene is approximately doubled by palmitic acid concentrations.²⁴ Another potent stimulator of UCP-3 is olive oil. After the various types of fat, there was an upregulating effect of olive oil on UCP-3 expression in muscle. The expression of the UCP-3 mRNA in muscle was significantly higher after an 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 tested.³³ The results of the data suggest that palm oil, olive oil and fish oils are better stimulators of UCP-3 production than saturated fats.¹⁷ 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 expression.²⁵ Mingrone and colleagues found a 35 percent reduction in UCP-3 protein levels in subjects having undergone gastric bypass surgery.²² 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 metabolism.²⁶ 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 is 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 reported that leucine supplementation during caloric restriction results in more fat loss and improves protein synthesis in muscle.³¹ Get ready for more exciting news on leucine and fat loss. It was recently shown that doubling leucine intake while on a high-calorie 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 tissues.³² So, leucine not only increases protein synthesis, but also reduces body fat 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.

References:

1. Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR, Kraemer HC, King AC. Comparison of the Atkins, Zone, Ornish and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA*, 2007 Mar 7;297(9):969-77.
2. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med*, 2004 May 18;140(10):769-77.
3. Cameron-Smith D, Burke LM, Angus DJ, Tunstall RJ, Cox GR, Bonen A, Hawley JA, Hargreaves M. A short-term, high-fat diet upregulates lipid metabolism and gene expression in human skeletal muscle. *Am J Clin Nutr*, 2003 Feb;77(2):313-8.
4. Pilegaard H, Osada T, Andersen LT, Helge JW, Saltin B, Neufer PD. Substrate availability and transcriptional regulation of metabolic genes in human skeletal muscle during recovery from exercise. *Metabolism*, 2005 Aug;54(8):1048-55.
5. Young ME, Goodwin GW, Ying J, et al. Regulation of cardiac and skeletal muscle malonyl-CoA decarboxylase by fatty acids. *Am J Physiol Endocrinol Metab*, 2001;280:E471-9.

6. Samec S, Seydoux J, Dulloo AG. Post-starvation gene expression of skeletal muscle uncoupling protein-2 and uncoupling protein-3 in response to dietary fat levels and fatty acid composition: a link with insulin resistance. *Diabetes*, 1999;48:436–41
7. Cameron-Smith D, Burke LM, Angus DJ, Tunstall RJ, Cox GR, Bonen A, Hawley JA, Hargreaves M. A short-term, high-fat diet upregulates lipid metabolism and gene expression in human skeletal muscle. *Am J Clin Nutr*, 2003 Feb;77(2):313-8.
8. Hirabara SM, Silveira LR, Abdulkader FR., Alberici LC, Procopio J, Carvalho CR, Pithon-Curi TC, Curi R. Role of fatty acids in the transition from anaerobic to aerobic metabolism in skeletal muscle during exercise. *Cell Biochem Funct*, 2006 Nov-Dec;24(6):475-81. Review.
9. Westerterp-Plantenga MS. The significance of protein in food intake and bodyweight regulation. *Curr Opin Clin Nutr Metab Care*, 2003;6:635–8.
10. Halton TL, Hu FB. The effects of high-protein diets on thermogenesis, satiety and weight loss: a critical review. *J Am Coll Nutr*, 2004;23:373–85.
11. Mikkelsen PB, Toubro S, Astrup A. Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein and carbohydrate. *Am J Clin Nutr*, 2000;72:1135–41.
12. Nedergaard J, Bengtsson T, Cannon B. Unexpected Evidence for Active Brown Adipose Tissue in Adult Humans. *Am J Physiol Endocrinol Metab*, 2007 May 1
13. Argyropoulos G, Harper ME. Uncoupling proteins and thermoregulation. *J Appl Physiol*, 2002 May;92(5):2187-98.
14. Krauss S, Zhang CY, Lowell BB. The mitochondrial uncoupling-protein homologues. *Nat Rev Mol Cell Biol*, 2005 Mar;6(3):248-61. Review.
15. Garruti G, Ricquier D. Analysis of uncoupling protein and its mRNA in adipose tissue deposits of adult humans. *Int J Obes Relat Metab Disord*, 1992 May;16(5):383-90.
16. Cortright RN, Zheng D, Jones JP, Fluckey JD, DiCarlo SE, Grujic D, Lowell BB, Dohm GL. Regulation of skeletal muscle UCP-2 and UCP-3 gene expression by exercise and denervation. *Am J Physiol*, 1999 Jan;276(1 Pt 1):E217-21.
17. Hirabara SM, Silveira LR, Alberici LC, Leandro CV, Lambertucci RH, Polimeno GC, Cury Boaventura MF, Procopio J, Vercesi AE, Curi R. Acute effect of fatty acids on metabolism and mitochondrial coupling in skeletal muscle. *Biochim Biophys Acta*, 2006 Jan;1757(1):57-66.
18. Gong DW, He Y, Karas M, Reitman M. Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, beta3-adrenergic agonists and leptin. *J Biol Chem*, 1997 Sep 26;272(39):24129-32.
19. Harper JA, Stuart JA, Jekabsons MB, Roussel D, Brindle KM, Dickinson K, Jones RB, Brand MD. Artificial uncoupling by uncoupling protein-3 in yeast mitochondria at the concentrations found in mouse and rat skeletal-muscle mitochondria. *Biochem J*, 2002 Jan 1;361(Pt 1):49-56.
20. Mills EM, Weaver KL, Abramson E, Pfeiffer M, Sprague JE. Influence of dietary fats on ecstasy-induced hyperthermia. *Br J Pharmacol*, 2007.
21. Costford SR, Chaudhry SN, Salkhordeh M, Harper ME. Effects of the presence, absence, and overexpression of uncoupling protein-3 on adiposity and fuel metabolism in congenic mice. *Am J Physiol Endocrinol Metab*, 2006 Jun;290(6):E1304-12.
22. Vettor R, Mingrone G, Manco M, Granzotto M, Milan G, Scarda A, Lombardi A, Greco AV, Federspil G. Reduced expression of uncoupling proteins-2 and -3 in adipose tissue in post-obese patients submitted to biliopancreatic diversion. *Eur J Endocrinol*, 2003 May;148(5):543-50.
23. Schrauwen P, Schaart G, Saris WH, Slieker LJ, Glatz JF, Vidal H, Blaak EE. The effect of weight reduction on skeletal muscle UCP-2 and UCP-3 mRNA expression and UCP3 protein content in Type II diabetic subjects. *Diabetologia*, 2000 Nov;43(11):1408-16.
24. Son C, Hosoda K, Matsuda J, Fujikura J, Yonemitsu S, Iwakura H, Masuzaki H, Ogawa Y, Hayashi T, Itoh H, Nishimura H, Inoue G, Yoshimasa Y, Yamori Y, Nakao K. Upregulation of uncoupling protein 3 gene expression by fatty acids and agonists for PPARs in L6 myotubes. *Endocrinology*, 2001 Oct;142(10):4189-94.

25. Sbraccia P, D'Adamo M, Leonetti F, Buongiorno A, Silecchia G, Basso MS, Tamburrano G, Lauro D, Federici M, Di Daniele N, Lauro R. Relationship between plasma free fatty acids and uncoupling protein-3 gene expression in skeletal muscle of obese subjects: in vitro evidence of a causal link. *Clin Endocrinol*, (Oxf), 2002 Aug;57(2):199-207.
26. Civitarese AE, Hesselink MK, Russell AP, Ravussin E, Schrauwen P. Glucose ingestion during exercise blunts exercise-induced gene expression of skeletal muscle fat oxidative genes. *Am J Physiol Endocrinol Metab*, 2005 Dec;289(6):E1023-9.
27. Schiffelers SLH, Blaak EE, Saris WHM, van Baak MA. In vivo β -adrenergic stimulation of human thermogenesis and lipid use. *Clin Pharmacol Ther*, 2000; 67: 558-566.
28. Bray GA. Calorigenic effect of human growth hormone in obesity. *J Clin Endocrinol Metab*, 29: 119-122.
29. Clapham JC, Arch JR. Thermogenic and metabolic antiobesity drugs: rationale and opportunities. *Diabetes Obes Metab*, 2007 May;9(3):259-75. Review.
30. Nagase I, Yoshida T, Saito M. Upregulation of uncoupling proteins by beta-adrenergic stimulation in L6 myotubes. *FEBS Lett*, 2001 Apr 13;494(3):175-80.
31. Donato J, Jr., Pedrosa RG, Cruzat VF, Pires IS, Tirapegui J: Effects of leucine supplementation on the body composition and protein status of rats submitted to food restriction. *Nutrition*, 22:520-527, 2006
32. Zhang Y, Guo K, LeBlanc RE, Loh D, Schwartz GJ, Yu YH. Increasing dietary leucine intake reduces diet-induced obesity and improves glucose and cholesterol metabolism in mice via multiple mechanisms. *Diabetes*, 2007 Jun;56(6):1647-54.
33. Rodriguez VM, Portillo MP, Pico C, Macarulla MT, Palou A. Olive oil feeding up-regulates uncoupling protein genes in rat brown adipose tissue and skeletal muscle. *Am J Clin Nutr*, 2002 Feb;75(2):213-20.
34. Boivin M, Camirand A, Carli F, Hoffer LJ, Silva JE. Uncoupling protein-2 and -3 messenger ribonucleic acids in adipose tissue and skeletal muscle of healthy males: variability, factors affecting expression, and relation to measures of metabolic rate. *J Clin Endocrinol Metab*, 2000 May;85(5):1975-83.
35. Colman E. Dinitrophenol and obesity: An early twentieth-century regulatory dilemma. *Regul Toxicol Pharmacol*, 2007 Jul;48(2):115-7. Epub 2007 Mar 31.
36. Bezaire V, Hofmann W, Kramer JK, Kozak LP, Harper ME: Effects of fasting on muscle mitochondrial energetics and fatty acid metabolism in Ucp3^{-/-} and wild-type mice. *Am J Physiol Endocrinol Metab*, 281 :E975-E982,2001.
37. Hesselink MK, Mensink M, Schrauwen P. Human uncoupling protein-3 and obesity: an update. *Obes Res*, 2003 Dec;11(12):1429-43. Review.
38. Kogure A, Sakane N, Takakura Y, Umekawa T, Yoshioka K, Nishino H, Yamamoto T, Kawada T, Yoshikawa T, Yoshida T. Effects of caffeine on the uncoupling protein family in obese yellow KK mice. *Clin Exp Pharmacol Physiol*, 2002 May-Jun;29(5-6):391-4.
39. Pedersen SB, Kristensen K, Fisker S, Jorgensen JO, Christiansen JS, Richelsen B. Regulation of uncoupling protein-2 and -3 by growth hormone in skeletal muscle and adipose tissue in growth hormone-deficient adults. *J Clin Endocrinol Metab*, 1999 Nov;84(11):4073-8.
40. Hioki C, Yoshida T, Kogure A, Takakura Y, Umekawa T, Yoshioka K, Shimatsu A, Yoshikawa T. Effects of growth hormone (GH) on mRNA levels of uncoupling proteins -, -2 and -3 in brown and white adipose tissues and skeletal muscle in obese mice. *Horm Metab Res*, 2004 Sep;36(9):607-13.