Athletes may soon be able to direct their metabolism to favor specific fuels to optimize body composition for a sport or for enhance performance. Comparatives sport studies have shown that major biochemical changes are possible. During its three-month winter sleep, the American Brown Bear undergoes a remarkable shift in metabolism which allows maximal utilization of fat stores and triggers a complete recycling of nitrogen and essential components of protein (63). This occurs without food or water intake and at near normal body temperatures, and the bear suffers no loss of bone or muscle. If starved at any other time of the year, bears lose more nitrogen than they take in (negative nitrogen balance), which reflects the sacrifice of a certain amount of lean mass for energy, just as humans do.

Although the mechanism of winter sleep metabolism is not known, there is no shortage of ideas on how to change fat metabolism in humans, nor of products purporting to effect this change. These include several products marketed to athletes to increase fat mobilization and utilization and to increase muscle mass. Of course, exercise can do that. The products which several drug companies are currently testing as anti-obesity agents mimic the effects of exercise by increased energy expenditure spent in heat production (thermogenesis) and fat breakdown (lipolysis). Such products would be quite useful to millions of obese Americans who are physically limited in their ability to safely exercise. Body conscious athletes are also likely to use these, especially body builders. In fact, many athletes already use related compounds such as clenbuterol and the newly available recombinant growth hormone, which is more expensive and involves nightly injections. Older Americans and body builders have been intrigued by the widely reported fat burning and muscle building properties of growth hormone, but since the cost is beyond the reach of most people, there is an intense interest in "growth hor-
mone releasers,” legal and inexpensive amino acids which allegedly have the same effects. L-carni-
tine is a third product sold to athletes to enhance “fat burning” and touted as producing “dramatic improvements in exercise capac-
ity.”

Do these three approaches increase fat utilization? And, are the drug effects of clenbuterol and growth hormone really achievable with “natural” supplements? One of these probably does work, one almost certainly does not and the last is questionable. The bad news for athletes is that nutritional ergogenic aids that really can enhance athletic performance are usually banned.

Beta-adrenergic agonist drugs stimulate sympathetic nervous system actions, typically produced by hormones such as adrenaline (epinephrine). Some adrenergic agonists can bind specifically to subgroups of cell membrane receptors, the protein which initiates a cellular effect when stimulated by the right hormone. Epinephrine (adrenaline) typically works on beta-adrenergic receptors, and norepinephrine tends to favor binding to alpha-adrenergic receptors. The actions resulting from these two main types of receptor activations can be very different and may even be opposite to each other (39, 40, 56). There are also subtypes classified on the basis of which drugs bind very specifically to a subtype without activating the others, except at higher doses. For example, B_1-
adrenergic agonists will increase heart rate and B_2-adrenergic ago-
nists will open up the airways (useful during an asthma attack). As the concentration of these agonists is increased, they tend to produce unwanted side effects because they stimulate other related adrenergic receptors.

These beta-adrenergic compounds are all related to epinephrine in their effects, a fat-
mobilizing hormone which is stimulated by exercise. This beta-
adrenergic effect has been demonstrated with small dialysis probes inserted directly into the subcuta-
neous fat tissue in normal living subjects during exercise (4). Because of the differences in the balance of adrenergic receptors, which are present in different regions of body fat, the effects of such stimulation also demonstrate regional variation. Thus, deep abdominal fat is the most sensitive to the lipolytic (fat burning) action, followed by subcutaneous abdomi-
nal fat, and then peripheral (but-
tocks, arms and legs) subcutaneous fat, for both men and women (3). Fat deposition appears to be pro-
moted in other sites in women through the opposite actions via adrenergic receptors (72). This means that exercise preferentially mobilizes abdominal fat in men and women, and presumably the beta-agonist compounds would do the same.

Pig farmers are familiar with a B_2-adrenergic agonist known as raclopamine that markedly increases the amount of lean mass and decreases the amount of fat produced per pound of feed, hence the general classification: nutrient repartitioning agent (43). Body builders are familiar with some closely related B_2-adrenergic agonists, clenbuterol and cimaterol (29). Cimaterol has been used primarily in lambs (13); clenbuterol is used in other animals such as chickens (28) and is used as an asthma drug in Europe (82). Body builders claim that clenbuterol enhances fat metabolism and increases lean mass in humans, although they have also noticed that some side effects such as tremors (69).

The various B_2-agonist repartitioning agents work differently among species, but the consistent effects of the related compounds raclopamine, cimaterol and clen-
buterol include direct inhibition of lipogenesis (fat production) and stimulation of lipolysis in adipose tissue (58, 64, 68), and increase of protein synthesis in muscle (10, 47, 65). In a sense, the most conv-
cincing evidence that these drugs work as nutrient repartitioning agents is that farmers use them; they are cost effective in producing desired effects for the intended animal species.

Recently a third type of Beta-
adrenergic receptor has been described (34). This B_3-receptor may be typified by an adrenergic receptor predominantly found in fat cells, although this is better under-
stood in the rat than in humans (1, 86). The presence of a distinct receptor with actions specific to lipolysis and thermoge-
nesis opens the possibility that a drug can be designed which works exclusively on these receptors without side effects, such as increased heart rate and tremors produced by currently available beta-adrenergic agonists. Several of the still unnamed drugs are reputed to have these effects, although human clinical trials have not yet been performed (50). There is evidence that some other B_3-agonists produce a desirable change in body composition, with a high rate of fat weight loss in humans (23). This effect occurs through an increased resting metabolic rate and thermic response to food (21, 54) and through appetite suppression.
An unknown substance labeled as clenbuterol is available to athletes through nutrition stores. Presumably, this is an inert substance since these retailers cannot legally sell the drug clenbuterol and athletes using the substance report no recognizable effects from its use. Clenbuterol is not a registered name and may be used on any product. However, the drug clenbuterol is a banned substance and is not one of the asthma medications allowed by the U.S. Olympic Committee (US Olympic Committee, Drug Hotline, 719-578-4574). It produces a positive drug test (26, 32). The USOC allows a few specific types of Beta-agonists to be used in inhalers by asthmatic athletes but these have to be declared in advance through medical channels.

**Ephedrine, caffeine and their natural sources**

Caffeine and ephedrine can increase resting metabolic rates and increase fat metabolism (7, 31). Presumably these work through separate mechanisms of phosphodiesterase inhibition (41) and Beta-adrenergic stimulation, respectively, although both of these substances also stimulate the release of catecholamines which will produce additional adrenergic actions. When administered together, the action of caffeine and ephedrine is greater than that expected from simply the sum effect of the two drugs and markedly enhances thermogenesis (8). There is also some unpublished data which suggests that this combination acts as a "nutrient repartitioning agent," increasing the proportion of muscle mass and reducing the total feed requirements in growing pigs (9). Supplements which include ephedrine and caffeine are being promoted to athletes as performance enhancers. Whether or not the concentration sold in various "natural" products can actually do anything has not been reported in any scientific study, but the athletes should be warned that these products may produce a positive drug test for banned substances (27).

Ephedrine is a beta-agonist with properties similar to amphetamines, but with somewhat less potency. Its use as an ergogenic aid, and the basis for its banning, is its stimulant properties. However, ephedrine also has a thermogenic effect (7) and appears to keep protein from being burned as fuel while maintaining the metabolic rate in semi-starved obese patients (67). Ephedrine is found in common over-the-counter decongestants and in some fairly exotic natural products, such as an herb known as Ma Huang and in a variety of teas which are brewed from related plant species (88). Ephedrine is a banned substance which can be readily detected by urinalysis (20).

The ergogenic potential of caffeine has been the subject of many studies and extensive reviews, many of which conclude that it is useful in endurance events such as marathon running because it spares glycolgen by increasing utilization of fatty acids (25, 35, 41, 53, 71). Not all studies have shown a performance benefit or an increase in circulating fatty acids (36), although this is partly related to previous habitual caffeine use (30, 37). Even relatively small doses of caffeine (100 mg) can stimulate metabolic rate; this could be particularly useful for weight maintenance among formerly obese individuals whose metabolic rates have slowed as a result of weight loss (31, 70).

Because of the potential ergogenic benefits, caffeine is also a banned substance, but only in urinary concentration greater than 12 ug/ml or 15 ug/ml, depending on the athletic organization (33). The upper range of urinary caffeine concentrations in heavy coffee drinkers is reportedly 4-8 ug/ml (19). A typical cup of freshly brewed coffee contains roughly 120 mg of caffeine. Studies demonstrating endurance benefits have used 250 to 330 mg (25, 59), while 350 mg produced highest levels in athletes at 9 ug/ml, with slightly lower levels after exercise (33). The concentrations which have been effective in producing fat loss in conjunction with ephedrine are considerably higher (200 mg, three times per day). Thus, ergogenic benefits for endurance events may be obtained at permissible and practical levels of coffee consumption, although a useful weight loss or weight maintenance effect in overweight subjects probably requires higher doses and the effects are more potent if caffeine is used in conjunction with ephedrine.

**Risks associated with beta-adrenergic agonists**

The health risks of the beta-agonist drugs are still unknown. Data has emerged in the past few years which hints that asthmatics may occasionally die as a consequence of beta-agonist drug use, although it is still unclear if this is more related to the heaviest use by the sickest patient. There are non-life threatening side effects, such as those observed in a Spanish poisoning epidemic that resulted from high levels of clenbuterol ingested in cooked beef.
liver (59); over 100 symptomatic cases were reported with symptoms of sleeplessness, headaches and tremors which lasted up to 48 hours. Nobody can anticipate the problems that will be encountered when athletes use these drugs in doses vastly exceeding the quantity prescribed for medical treatment. One cyclist reportedly died as a possible consequence of ephedrine use (24).

**Growth hormone and body composition**

Growth hormone is an important metabolic regulator which does far more than simply produce longitudinal growth in children. One role is as a counter regulatory hormone which compensates for the effects of insulin and maintains blood sugar levels. In excess, growth hormone produces hyperglycemia and other metabolic abnormalities which require medical treatment. Growth hormone is used by athletes because it stimulates protein synthesis and decreases body fat, at least in men deficient in growth hormones (22). Studies with the new recombinant human growth hormone (rhGH) and recombinant insulin-like growth factor-1 (IGF-1) also demonstrate applications in the restoration of lean mass in catabolic patients (48, 84) and these have led to new interest in growth hormones for dieters, the weak, the elderly and athletes alike. Since the supply of these newly available substances is controlled, purveyors of nutritional supplements promote “growth hormone releasers,” primarily the amino acids arginine and ornithine, as an alternative approach to producing the same effects. What are these rhGH effects and what is the evidence for efficacy of growth hormone releasers?

A study with 12 relatively young growth-hormone deficient men injected with nightly doses of rhGH for six months found no net change in body weight, but there was an average 12 pound decline in fat weight, with equal increases in fat-free weight, as measured by K40 counting and corroborated by anthropometric changes (76). The treatment also produced an increase in resting metabolic rate, compared to baseline and to a placebo treatment group. Another study with young men treated daily for four months resulted in moderate increases in thigh muscle volume (with no change in quadriceps isometric strength) and decreases in fat volume, measured by computed-tomography (55). A separate research group studied elderly men receiving rhGH for six months and obtained similar body composition results (74). There are several key points which have been inadequately presented to the public concerning these reports. First, these studies involved abnormal subjects, selected for growth hormone deficiency, or IGF-1 deficiency, which is typical of only a minority of elderly men. So far, no similar long-term study has been performed on normal active men or women. Second, the magnitude of change in body composition obtained by these treatments with nightly injections is hardly worth the cost (estimated at $13,800 per year for one study) compared, for example, to the substantial and comprehensive benefits which might be obtained if this money was invested in exercise equipment and a personal trainer. Perhaps the deficient men in these studies would not modify body composition in response to exercise as readily as normal men. On the other hand, exercise is a well known stimulator of growth hormone release (57) and might be beneficial in restoring growth hormone levels in otherwise healthy elderly men with diminished secretion rates. Third, while growth hormone replacement decrease lipogenesis, it also promotes a redistribution of fat from abdominal to a more peripheral distribution that is typically more feminine than masculine (73, 87). The question remains, what will rhGH do for normal men and women?

Administered to obese women during 14 weeks of dietary restriction, rhGH helped to preserve fat-free mass but without enhancing fat reduction (79). Thus, even with substantial caloric deprivation (12 kcal/kg ideal body weight), supplemental growth hormone can still promote increases in circulating IGF-1 and improve nitrogen balance. This suggests that rhGH treatment would be most useful in patients losing body mass, with only limited usefulness in healthy subjects trying to modify body composition.

**Growth hormone releasers**

Are amino acid “growth hormone releasers” an effective alternative to the high cost and limited availability of rhGH and IGF-1? The theory behind growth hormone releasers originated from a diagnostic test used by endocrinologists to assess growth hormone response. Arginine infusion produces a relatively reproducible increase in growth hormone secretion in normal subjects (60). The leap of faith from a short term rise in hormone produced by an arginine challenge test to the assumption that oral administration of arginine will produce this same response has been tested in only a
few limited studies. One study found that 1200 mg of L-lysine and 1200 mg of L-arginine provoked a consistent rise in growth hormone in young men, but neither one of these amino acids produced a response when administered alone (52); these results remain unexplained. A sleep study indicated that the normal nocturnal rise in growth hormone was significantly increased after a week of low dose arginine and aspartate administration (9250 mg/day) to healthy young men (14).

An NSCA-funded study examined the effect of 10 days of oral arginine (0.1 g/kg body weight) with a low calorie diet on body composition and muscle strength measures and found no difference between placebo and arginine treated weight lifters (46).

One careful study examined the response of growth hormone to oral administration of ornithine (16). When given by infusion, ornithine is reportedly three times as potent as arginine in its growth hormone stimulation. Three doses: 40, 100, and 170 mg/kg body weight (approximately 3, 7 and 12 g ornithine per 155 pound man) were administered to male body builders. All doses produced measurable increases in serum ornithine, but only the highest dose produced a significant rise in some growth hormone, an average of approximately 9 ng/ml, after 90 minutes. This is still less than the typical rise observed during sleep in normal people and the authors question the significance of this brief daytime rise. The greatest problem was that the oral dose, which produced a growth hormone response, and caused stomach cramps and diarrhea in all nine subjects. Such a stressor is capable of inducing a growth hormone response by itself, and conceivably, this rise is not even directly related to an ornithine stimulation.

It is questionable whether amino acids can promote a growth hormone response at tolerated oral doses, and if a rise in growth hormone will be meaningful in terms of IGF-1 stimulation and any body composition or ergogenic benefit in normal subjects. The reasonable conclusion from the available data is that athletes should not waste any money on these supplements.

**L-carnitine: Vitamin B<sub>T</sub>**

Carnitine was briefly labelled as a vitamin, (vitamin B<sub>T</sub>) when it was discovered that this was an essential factor in the diet of the Tenebrio beetle. When mealworms (Tenebrio larvae) are starved without carnitine supplementation, they die without being able to use their fat stores. Carnitine is also very important for fat metabolism in the non-insect world, but most animals, including humans, synthesize their own from essential amino acids. The human carnitine requirement is satisfied by both dietary and internally synthesized carnitine. The best dietary source of carnitine is red meat. Carnitine is synthesized primarily in the liver and kidneys and over 90 percent of carnitine resides in heart and skeletal muscles. Humans with a rare genetic carnitine deficiency have an impaired ability to oxidize fatty acids and suffer from muscle weakness, hypoglycemia, and reduced ability to increase the formation of ketone bodies during fasting. Some, but not all of these deficient patients benefit from supplementation (15, 61).

The interest in carnitine as an ergogenic aid revolves around its best known physiological role in the transport of long chain fatty acids into the mitochondria for energy production. If the activity of the mitochondrial membrane enzyme could be increased by raising intramuscular concentrations of carnitine, fatty acid oxidation might be increased. Then, theoretically, carnitine could be valuable as a carbohydrate sparing agent in endurance events.

The problem with this line of reasoning is that more, if it can be achieved, is not necessarily better. One hypothesis for the function of carnitine in high intensity exercise conditions is to act as a sink for excess acetyl CoA. This is quite separate from its other function of transporting long chain fatty acids across mitochondrial membranes. A decrease in carnitine may limit additional transport of fatty acids into the mitochondria, thus slowing the oxidation of fat at a time when oxygen may be deficient and fatty acids may not be the optimal fuel (45, 75). Thus, a deficiency causes problems because mitochondrial membrane transport of some fatty acids does not occur, but artificially increasing carnitine levels in normal muscle might override a physiologic regulation to prevent transfer of unneeded additional acetyl CoA into the mitochondria and also potentially damage mitochondrial membranes (45).

The second problem with supplementing with carnitine to burn more fat is that more usually is required to alter a physiological system than simply supplementation of an enzyme or a cofactor. For critical regulatory steps, there are generally a series of checks
and balances. If this were not the case, our metabolism would run amuck with every meal. An example of such a balancer, malonyl-CoA, is an intermediate in lipid metabolism which inhibits carnitine-dependent transport of fatty acids into mitochondria (12).

Actually getting carnitine into the muscle is another problem. The upper limits of intestinal absorption are achieved at a 2 gram oral dose in normal subjects (44). Reasonable calculations suggest that such a dose would actually increase carnitine content in normal resting muscle by only 1-2 percent (51); thus, there may be a problem getting enough carnitine into the muscle to have any substantial effect.

Athletes using carnitine supplements could even induce a muscle carnitine deficiency. Several animal studies have deliberately reproduced muscle carnitine deficiency by administering D-carnitine in place of L-carnitine (62). Myasthenia was accidentally induced in several renal dialysis patients in a experiment designed to study the lipid lowering ability of carnitine supplements; the patients were treated with a racemic mixture (both D- and L-forms) of carnitine and because their kidneys did not normally excrete the inactive D-carnitine, it accumulated in levels which produced neuromuscular abnormalities by competing with the active L-form for binding sites on the acyltransferase enzymes (11).

There is no evidence that athletes become carnitine deficient with training. During high intensity exercise, muscle free carnitine declines as it combines with acetyl-CoA (38, 49, 75), but little or no carnitine is actually lost from the muscle during exercise (18, 49, 75). Six months of training by distance runners and sprinters produced only small reductions in resting muscle or serum levels of carnitine; supplementation of L-carnitine (1 gram/day for 120 days) produced only small changes over baseline muscle carnitine levels (2). Only the supplemented distance runners demonstrated an exercise induced increase in serum carnitine levels; supplemented sprinters and distance runners were otherwise different from unsupplemented runners only in having higher urinary carnitine excretion rates.

If there is no deficiency in athletes, does carnitine supplementation nevertheless increase the utilization of fatty acids and does this enhance any type of athletic performance? Four recent studies from four countries have examined this question using cycle ergometer protocols. Three placebo controlled studies, with administration of L-carnitine at 1 g/day for 28 days, 2 g/day for 28 days or 5 g/day for five days found no benefit in maximal oxygen uptake, in endurance performance, or significant changes in any metabolic markers (42, 66, 81). The only recent study which has reported positive effects of L-carnitine supplementation used a single 2 g dose one to two hours before maximal exercise by moderately trained men on a cycle ergometer. This reportedly reduced plasma lactate and pyruvate (77) and significantly increased maximal oxygen uptake (+8 percent) and power output (+17 percent) (83). In another recent study, 3 g/day for seven days of L-carnitine supplementation produced markedly lower respiratory quotients during treadmill running in normoxic or hypoxic conditions, suggesting a reduction in carbohydrate utilization (85).

The suggesting a performance benefit through enhancement of skeletal muscle utilization of fatty acids is weak. The positive studies are a minority among several other good studies which more typically have found no change in fatty acid utilization or in endurance performance. Animal studies with treadmill exercised rats have also consistently reported no alterations in energy metabolism (e.g. 5, 78). Body composition is also clearly not affected by L-carnitine supplementation. In one interesting study, regular treadmill exercise nearly doubled the rate of fat turnover in rats, while L-carnitine supplementation had no effect whatsoever on fat stores (6). Thus, L-carnitine is not a substance to recommend to any athlete at this time, even though there is no defined health risk or legal issue associated with its use as a supplement.

Conclusions

Although the bears' winter sleep phenomenon cannot be duplicated, there are some drugs and naturally occurring substances which are probably effective in reducing fat stores and increasing, or at least maintaining, protein synthesis. Beta-agonists produce changes in body composition similar to those caused by exercise. This includes epinephrine in combination with caffeine; both of these substances can be found in natural products, but both can produce positive drug tests for banned substances. There is not much reason to believe that amino acid supplements produce any beneficial changes through growth hormone stimulation. The dose of ornithine which is effective in producing a temporary rise in growth hormone overlaps the dose range with unac-
ceptable side effects of gastrointestinal distress and even this rise may not be physiologically meaningful. Furthermore, there is currently no proof that increasing growth hormone levels in normal men and women will produce desired alterations in body composition. The extreme of excess growth hormone secretion is a medical condition which requires treatment. L-carnitine continues to intrigue physiologists because of its key role in fatty acid oxidation. However, current data does not suggest that this will be useful to endurance athletes as a glycogen-sparing aid or that it will produce any change in fat stores.

There may be a risk in the fat reduction itself, as athletes find ways to alter metabolism and perhaps lose fat to the exclusion of all other tissues, it is likely important and previously unrecognized essential roles for fat at the lowest end of achievable body fat will be discovered.

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