Dietary Fat Intake, Supplements, and Weight Loss

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Abstract/Résumé

Although there remains controversy regarding the role of macronutrient balance in the etiology of obesity, the consumption of high-fat diets appears to be strongly implicated in its development. Evidence that fat oxidation does not adjust rapidly to acute increases in dietary fat, as well as a decreased capacity to oxidize fat in the postprandial state in the obese, suggest that diets high in fat may lead to the accumulation of fat stores. Novel data is also presented suggesting that in rodents, high-fat diets may lead to the development of leptin resistance in skeletal muscle and subsequent accumulations of muscle triacylglycerol. Nevertheless, several current fad diets recommend drastically reduced carbohydrate intake, with a concurrent increase in fat content. Such recommendations are based on the underlying assumption that by reducing circulating insulin levels, lipolysis and lipid oxidation will be enhanced and fat storage reduced. Numerous supplements are purported to increase fat oxidation (carnitine, conjugated linoleic acid), increase metabolic rate (ephedrine, pyruvate), or inhibit hepatic lipogenesis (hydroxycitrate). All of these compounds are currently marketed in supplemental form to increase weight loss, but few have actually been shown to be effective in scientific studies. To date, there is little or no evidence supporting that carnitine or hydroxycitrate supplementation are of any value for weight loss in humans. Supplements such as pyruvate have been shown to be effective at high dosages, but there is little mechanistic information to explain its purported effect or data to indicate its effectiveness at lower dosages. Conjugated linoleic acid has been shown to stimulate fat utilization and decrease body fat content in mice but has not been tested in humans. The effects of ephedrine, in conjunction with methylxanthines and aspirin, in humans appears

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unequivocal but includes various cardiovascular side effects. None of these compounds have been tested for their effectiveness or safety over prolonged periods of time.

Malgré la controverse au sujet du rôle de l'équilibre des nutriments dans l'étiologie de l'obésité, la consommation d'aliments riches en gras semble fortement associée à cet état. Du fait que l'oxydation des graisses ne s'adapte pas rapidement à l'augmentation de la consommation de graisses et que la capacité d'oxyder les graisses après un repas est plus faible chez l'obèse, les régimes hyperlipidiques peuvent favoriser l'augmentation des réserves de graisses. D'après des études récentes, les régimes hyperlipidiques semblent augmenter la résistance de la leptine dans le muscle squelettique des rongeurs et, par conséquent, la concentration musculaire de triacylglycérol augmente. Malgré cela, quelques régimes à la mode incorporent une forte diminution de la consommation d'hydrates de carbone, d'où l'augmentation du contenu alimentaire des graisses. De telles directives sont basées sur le principe suivant : en réduisant la concentration sanguine d'insuline, on augmente la lipolyse et l'oxydation des graisses et on abaisse les réserves de graisses. De nombreux suppléments sont censés augmenter l'oxydation des graisses (carnitine, acide linoléique conjugué), accroître le métabolisme (éphédrine, pyruvate) ou inhiber la lipogenèse hépatique (hydroxycitrate). Toutes ces substances sont commercialisées sous forme de supplément conçu pour favoriser la perte de poids mais peu nombreuses sont celles dont les effets ont été démontrés scientifiquement. Dans l'état de nos connaissances actuelles, il y a peu ou pas d'évidence chez les humains concernant les effets amaigrissants de la carnitine et de l'hydroxycitrate. Le pyruvate semble efficace à forte dose mais on n'en connaît pas le mécanisme ni les effets à faible dose. L'acide linoléique conjugué stimule l'utilisation des graisses et la réduction des graisses chez la souris mais son effet n'a pas été démontré chez les êtres humains. Les effets de l'éphédrine combiné aux méthylxanthines et à l'aspirine semblent sans équivoque mais les effets secondaires portent sur l'appareil cardiovasculaire. L'efficacité et l'innocuité à long terme de ces substances n'ont pas été encore démontrés.

Introduction

Despite heightened public awareness of the many health risks associated with obesity, the prevalence of obesity in North Americans continues to increase. It has recently been estimated that approximately one third of adults (Kuczmarksi et al., 1994), and one quarter of children and adolescents are overweight (Troiano et al., 1995). In particular, visceral obesity is associated with a greater risk of cardiovascular disease (Donahue et al., 1987; Folsom et al., 1993; Larsson et al., 1984) and insulin-independent diabetes (Colditz et al., 1995). In addition, social pressures promoting a fashionable lean appearance continue to increase. Although the associated health risks and social stigma associated with increased body fat are clearly of greatest concern to overweight individuals, it should be noted that many athletes are also highly conscious of body mass. In particular, athletes such as figure skaters and dancers are concerned with aesthetic appearance, while weight lifters and wrestlers may wish to lose weight to achieve a lower competitive weight class.

It is obvious that the increased prevalence of obesity to near epidemic proportions, despite an acute public awareness to this problem, has fueled the financial gain of an industry promoting special diets and dietary supplements as a means to lose unwanted body fat. Why does the incidence of obesity continue to rise despite public awareness of this situation and the rhetoric of health care professionals

advocating exercise and a balanced diet emphasizing complex carbohydrates (CHO)? Clever marketing strategies would lead us to believe that such traditional strategies are doomed to failure and that only through special diets and supplements can we hope to lose weight. Among the many current popular remedies are supplements containing caffeine, ephedrine, pyruvate, carnitine, hydroxycitrate, conjugated linoleic acid, and chromium, as well as diets emphasizing the reduction of CHO intake (Protein Power, Zone Diet) to promote fat loss. This review will examine the role of macronutrient balance and various popular weight loss supplements in controlling body composition. Pharmacological agents, appetite suppressants, and fat absorption blockers, while potentially significant factors in controlling body composition, are beyond the realm of this review.

Macronutrient Balance: Does Fat Make You Fat?

MACRONUTRIENTS AND THERMIC EFFECTS

In spite of potentially large variations in daily energy intake and expenditure, body mass is generally tightly maintained over periods of months to years. Macronutrient (CHO, fat, and protein) balance can significantly influence energy intake and is, therefore, a potentially important factor in maintaining a neutral energy balance over prolonged periods of time. However, there still remains considerable controversy regarding the role of dietary fat in the development of obesity (Bray and Popkin, 1998; Willett, 1998). Clearly, excessive energy intake from all sources and the decline of physical activity must also be addressed to understand the increase in global obesity.

It is generally thought that dietary composition has little bearing on overall energy expenditure. Assuming a thermic effect of 20, 8, and 2% for protein, CHO, and fat, respectively, it can be calculated that an individual consuming 2,500 kcal/d of a low-fat diet (20% fat, 20% protein, 60% CHO) will expend 230 kcal/d due to the thermic effect of food alone (Hill et al., 1993). Increasing the fat content to 40% and lowering the CHO content to 40% would reduce the thermic effect to 200 kcal/d. This difference of 30 kcal/d would be equivalent to 10,950 kcal per year, or only 1.5 kg (3.1 lb.) of body fat. However, these calculations assume a constant protein consumption (~20%), which, for example, is lower than that recommended by several popular current diets (Zone Diet, Protein Power) advocating a protein intake of 30% kcal or greater. For the same 2,500 kcal/d diet, increasing the protein content to 30% and adjusting the fat and CHO intakes to 20 and 50%, respectively, would increase the thermic effect to 270 kcal/d, or 70 kcal/d greater than the previously mentioned high-fat diet. This would result in an additional expenditure of 3.3 kg, or 7.3 lb per year, an amount that can hardly be considered trivial.

MACRONUTRIENTS AND ENERGY INTAKE

In spite of the small but potentially significant role of macronutrient composition in altering energy expenditure through the thermic effect of food, it has generally been considered that the greatest influence of altering the macronutrient balance is to modulate energy intake. Several studies have demonstrated that increasing dietary caloric density by elevating fat content results in a spontaneous increase in energy intake (Kendall et al., 1991; Lissner et al., 1987; Proserpi et al., 1997;

Stubbs et al., 1995; Thomas et al., 1992; Tremblay et al., 1991; Tremblay et al., 1989; Westerterp et al., 1996) and resultant weight gain (Kendall et al., 1991; Lissner et al., 1987; Tremblay et al., 1989; Westerterp et al., 1996). However, if the caloric density of high-fat diets is made equal to that of low fat diets by dilution with water, differences in energy consumption and subsequent changes in body mass are minimized (Lewis et al., 1977; Saltzman et al., 1997; van Stratum et al., 1978). These data suggest that individuals consuming a high calorie diet gain weight due to the inabilty to compensate by reducing the volume of food intake.

The reasons for the incomplete compensation are not entirely clear. Flatt u (1987b) hypothesized that a drive to maintain CHO balance (storage and oxidation) was a major factor in regulating energy intake. Thus, diets low in CHO may have to be consumed in relatively greater amounts in order to maintain CHO balance. This has been demonstrated in mice that increase their energy intake the day after CHO depletion (Flatt, 1987a). However, in humans, consuming either depletion (3% kcal CHO) or control (47% kcal CHO) isocaloric diets for 1 day does not affect ad libitum food intake the subsequent day (Stubbs et al., 1993). In addition, due to the relatively low amount of free glucose that can be stored in the blood (5 g), it is necessary for the CHO in a typical meal (50–150 g) to first be stored as glycogen in muscle and liver cells prior to being released for oxidation (~10 g of glucose/hr in the post prandial state). Thus, Flatt (1995) has hypothesized that glucose oxidation is promoted after the filling of the glycogen stores and, conversely, that lowering glycogen stores would favor the oxidation of FFA. Evidence for this phenomenon has been provided by the studies of Schrauwen and colleagues (1997a, 1998) who demonstrated that the adaptation of FFA oxidation to a high-fat diet in both lean and obese individuals occurred very rapidly (i.e., within 24 hr) if glycogen stores were first depleted with exhaustive exercise. It is important to note, however, than even in lean individuals, the ability to match fat oxidation to intake in the absence of glycogen depletion is not instantaneous and requires 4 to 7 days (Schrauwen et al., 1997b; Smith et al., 2000). This is in direct contrast to the ability to immediately adjust CHO oxidation rates to match intake (Abbott et al., 1988; Acheson et al., 1988). Thus, an inability for obese or obese-prone individuals to rapidly adjust rates of fat oxidation to match intake, particularly in the absence of regular glycogen-depleting exercise, may lead to the accumulation of body fat.

IMPAIRED LIPID OXIDATION IN THE OBESE: CONTRAINDICATION FOR A HIGH-FAT DIET

There is a clear association between obesity and the development of non-insulin dependent diabetes (Kannel et al., 1996). Acutely, insulin resistance can be induced following an intravenous administration of Intralipid (Boden and Chen, 1999), while the overnight lowering of plasma FFA with acipimox significantly improves insulin sensitivity (Santomauro et al., 1999). In the 1960s, Randle and colleagues hypothesized that the observed impairment in glucose utilization in obesity and diabetes was due to elevated plasma FFA and subsequent oxidation (Garland et al., 1964; Garland and Randle 1964; Newsholme and Randle 1964; Randle et al., 1963; Randle et al., 1964). It was demonstrated in vitro that subsequent to increased FFA availability and oxidation, intracellular citrate and acetyl CoA/CoA became elevated,

resulting in the inhibition of phosphofructokinase (PFK) and pyruvate dehydrogenase (PDH), respectively (Dobson et al., 1986; Garland et al., 1963; Hagg et al., 1976; Taylor and Halperin, 1973), and subsequent down-regulation of glycolysis. Despite the apparent association between increased plasma lipid availability and decreased CHO utilization, recent evidence has suggested that lipid metabolism may, in fact, be *impaired* in skeletal muscle from the obese. The depression in the ratio of aerobic (citrate synthase, β-hydroxyacyl-CoA dehydrogenase) to glycolytic (PFK) activity (Simoneau and Kelley, 1997) and carnitine palmitoyl transferase (CPT) I (Kelley et al., 1999) has been demonstrated in muscle from obese humans. Correspondingly, FFA oxidation in the fasted state in resting forearm (Kelley and Simoneau, 1994) and thigh muscles (Kelley et al., 1999) of the obese have also been shown to be depressed. Impaired whole-body lipid oxidation has also been demonstrated in obese Zucker rats (Torgan et al., 1990).

Interestingly, it has been shown recently in obese humans that despite their general state of insulin resistance, oxidation of FFA across the thigh muscles *is not impaired during insulin infusion* (Kelley and Simoneau, 1994). This has also been demonstrated in rodents (Muoio et al., 1999). Thus, it would be expected that the elevated plasma insulin and FFA levels seen in obesity and diabetes would result in enhanced intramuscular TG storage, which shows a strong correlation to insulin resistance (Kazunori et al., 1997; Koyama et al., 1997; Pan et al., 1997). Using the dual-label pulse-chase procedure, we have recently demonstrated in isolated, contracting soleus muscle, a repartitioning of palmitate toward TG synthesis and away from oxidation in obese Zucker rats (Figure 1).

Thus, considering the relative insensitivity of the body to adjust lipid oxidation to match intake in the absence of exercise and the impaired ability to oxidize FFA in skeletal muscle of the obese-prone, low-CHO/high-fat diets would appear to be contraindicated. Furthermore, we have recently completed experiments providing the first direct evidence that leptin resistance in skeletal muscle can be induced with high-fat diets. Leptin has been demonstrated to stimulate FFA oxidation and

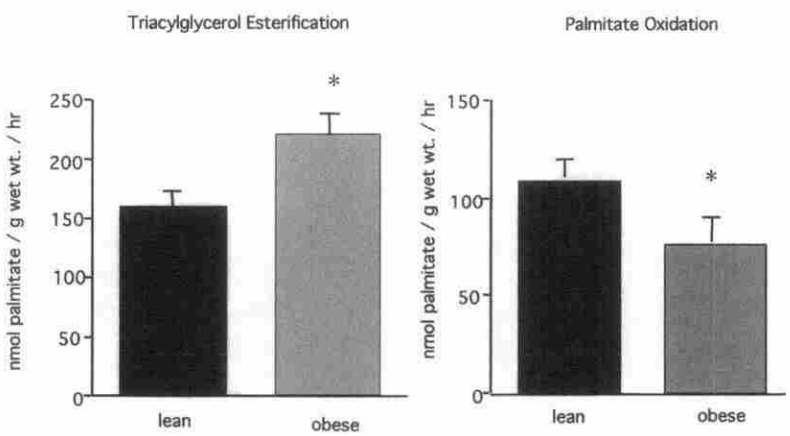

Figure 1. Incorporation of [9, 10 ^{3}H]-palmitate into triacylglycerol and oxidation in lean and obese Zucker rats. *significantly different from lean.

to blunt the synthesis of TG in skeletal muscle (Muoio et al., 1997; Muoio et al., 1999). We have confirmed these findings, as well as to demonstrate that leptin also stimulates TG hydrolysis, as has been previously shown in pancreatic islet cells (Shimabukuro et al., 1997). However, in isolated soleus muscles from rats fed diets containing 60% kcal lipid (safflower oil, n-3 fatty acids) for 4 weeks, leptin failed to repartition incorporated FFA toward oxidation and away from esterification, or to stimulate TG hydrolysis (Figure 2). Thus, high-fat diets may induce leptin resistance, leading to a decrease in the rate of lipid oxidation and a subsequent accumulation of muscle TG (Steinberg and Dyck, in press). This may be a significant factor in the development of obesity and diabetes. However, further research in this area is clearly needed before any conclusions can be made.

USE OF LOW-CHO DIETS

Many of the current diet trends advocate a decrease in dietary CHO and an increase in the proportion of lipid and protein (Protein Power, Zone Diet, etc.). This approach is rationalized on the premise that a reduced CHO intake will decrease circulating insulin concentrations, thereby promoting adipocyte lipolysis and oxidation of FFA by skeletal muscle. However, lipolysis does not appear to be impaired in the obese. Ranneries and colleagues (1998) demonstrated that both at rest and during moderately intense aerobic exercise, lipolysis (as measured by arterial glycerol), was not reduced in previously obese relative to lean individuals (Figure 3). However, the magnitude of plasma FFA accumulation was significantly greater in the obese during exercise, suggesting a reduced clearance of FFA by muscle. Furthermore, if the calculated rates of lipid oxidation from this study are plotted as a function of the arterial FFA concentration, it is clear that lipid oxidation is significantly reduced for a given arterial supply of FFA (Figure 4). Thus, the lowering of plasma insulin following a diet with a lower CHO content may be an important factor to increase whole-body lipid oxidation and decrease storage in the muscle of obese individuals. It has recently been suggested by Graham and

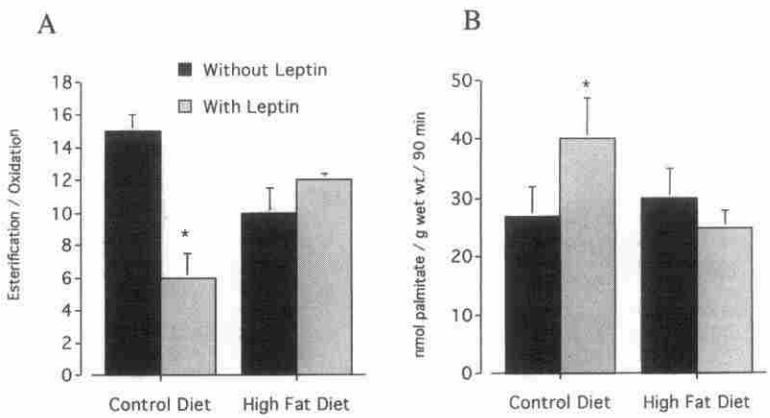

Figure 2. The effect of leptin on (A) the ratio of palmitate esterification to oxidation, and (B) triacylglycerol hydrolysis in isolated rat soleus following 4 weeks of control or high-fat diets. *significantly different from control group.

Adamo (1999) that the practice of consuming a CHO-rich diet in inactive individuals may lead to unhealthy consequences, and a balance of 50/30/20% (CHO/fat/protein) may be more desirable. Increases in plasma TG in healthy, inactive individuals after 10 days of a diet containing 60% kcal CHO has been documented (Coulston et al., 1983), which is due to decreased VLDL-TG clearance by the liver (Parks and Hellerstein 2000; Parks et al., 1999).

Although several studies have examined the effects of high-protein/low-CHO diets on weight loss and body composition, the majority of these studies have

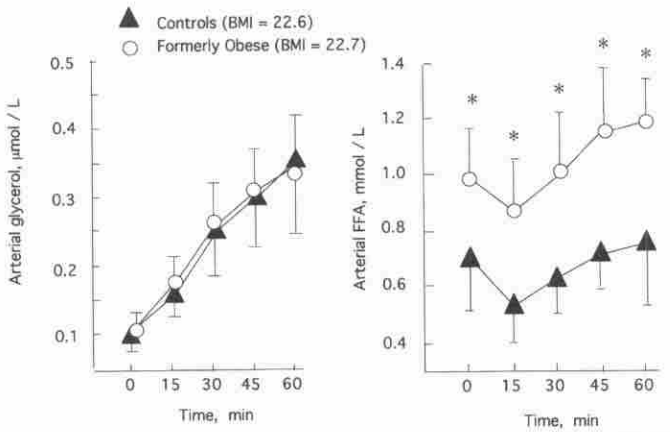

Figure 3. Arterial glycerol and FFA levels at rest and during cycling in lean and formerly obese individuals. *significantly different from controls. Modified from Ranneries et al. (1998), **A.J.P.** 274: E155.

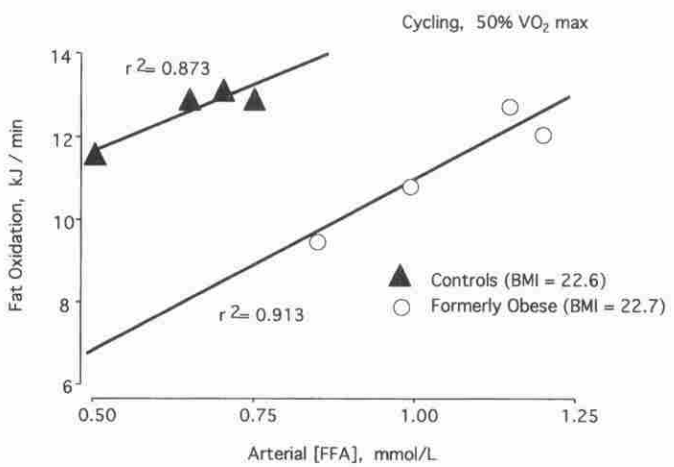

Figure 4. Lipid oxidation at rest and during cycling in lean and formely obese individuals. Data from Ranneries et al. (1998), **A.J.P.** 274: E155.

utilized diets that are very low in calories (i.e., 420–800 kcal/d; Barrows and Snook 1987; Brown et al., 1983; Hendler and Bonde 1988; Stallings and Pencharz 1992; Vazquez et al. 1995; Willi et al., 1998), and CHO content (i.e., <15%; Hendler and Bonde 1988; Stallings and Pencharz 1992; Vazquez et al., 1995; Willi et al., 1998; Worthington and Taylor 1974). While many of these studies have demonstrated significant body weight and fat loss on high-protein diets, several did not include a control diet for comparison (Barrows and Snook 1987; Brown et al., 1983; Stallings and Pencharz 1992; Willi et al., 1998). Furthermore, at least one study has not found a beneficial effect on weight loss of increasing protein content in a low caloric diet (Hendler and Bonde 1988). However, a recent study by Skov and colleagues (1999) found a beneficial effect on loss of body weight and fat when protein content was increased from 12 to 25% on an ad libitum diet. Dietary CHO content was maintained between 45 and 58% kcal. It should be noted that none of these studies included an exercise component. Furthermore, there is also no evidence to indicate that whole-body lipid oxidation is improved when consuming a low-CHO diet. Therefore, due to the extreme conditions imposed in the majority of these studies and the lack of mechanistic information, it is difficult to extrapolate the potential weight loss benefits of a high-protein/low-CHO diet to more normal situations. Clearly, additional research investigating the merit of reduced CHO diets in the maintenance of body weight is warranted.

Can Supplements Increase Muscle FFA Utilization?

If an impaired ability to oxidize FFA in skeletal muscle is a contributing factor to the development of obesity and increased muscle TG concentrations leading to the development of insulin resistance, then supplements that promote FFA oxidation in muscle may be of value in treating obesity. Supplements containing carnitine and conjugated linoleic acid have been proposed to be beneficial in this area.

CARNITINE

Carnitine is produced endogenously in the liver and kidney from its precursors, methionine and lysine, and is also obtained through dietary sources such as red meat and dairy products. Carnitine is a required cosubstrate for the conversion of fatty-acyl CoA to fatty acyl carnitine at the inner surface of the outer mitochondrial membrane (Figure 5). Fatty acyl carnitine is subsequently translocated to the mitochondrial matrix, where it is reconverted to fatty-acyl CoA to undergo β-oxidation. The activity of CPTI is considered rate-limiting for the oxidation of long-chain fatty acids (McGarry, 1995). The fact that muscle CPT activity is reduced in obesity (Kelley et al., 1999) and that defects in the CPT transport system are associated with muscle lipid accumulation (Shumate et al., 1982) suggests that increasing muscle carnitine content may be beneficial to overweight individuals.

The vast majority of the literature pertaining to the use of carnitine as a supplement is concerned with its use as an ergogenic aid and not as a weight loss product. Nevertheless, carnitine is marketed as a "fat burner" and routinely promoted in health food stores as an adjunct to weight loss programs. It should also be noted that elevated muscle carnitine levels would theoretically increase the formation of acetylcarnitine, thereby reducing mitochondrial acetyl CoA levels. The result

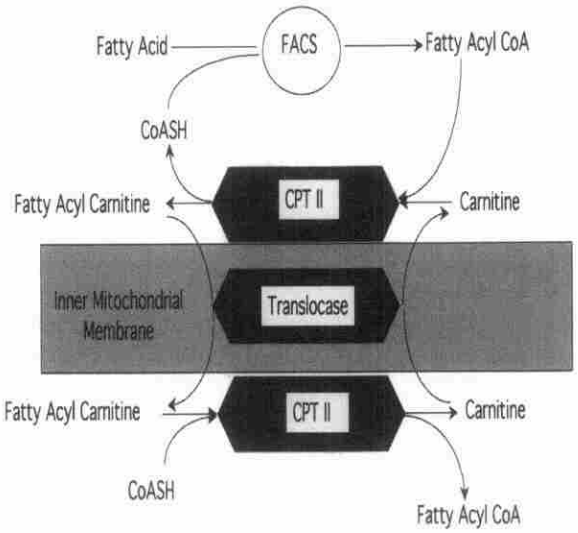

Figure 5. Schematic of FFA transport across the inner mitochondrial membrane. CPT, carnitine palmitoyl transferase; FACS, fatty acyl CoA synthase.

of a reduced acetyl CoA/CoA ratio is a stimulation of PDH and increased glucose oxidation. Thus, the potential exists for increased muscle carnitine levels to actually decrease the rate of lipid oxidation, which is often overlooked when advocating carnitine as a fat burner.

It is obvious that in order for carnitine to have any effect on FFA flux into muscle mitochondria, its content in the muscle must first be elevated. Studies using rodents have documented 36 to 81% increases in muscle carnitine content following supplemental dosages of 5 to 100 mg/kg body weight for 3 to 10 days (Decombaz et al., 1987; Decombaz et al., 1990). However, an acute infusion of carnitine into dogs (0.15 mmol/kg) resulting in a 14-fold increase in plasma carnitine did not increase muscle carnitine content (Dubelaar et al., 1991), indicating that several days are required to sufficiently increase muscle levels. In humans, supplementation with 2 to 6 g/d, for 5 to 14 days results in a plasma carnitine elevation of 40 to 100% (Siliprandi et al., 1990; Soop et al., 1988; Trappe et al., 1994). However, few human studies have measured muscle carnitine content after supplementation and have shown little to no increase (Arenas et al., 1991; Vukovich et al., 1994) in total muscle carnitine content or in CPTI activity (Arenas et al., 1994). Indeed, this should come as little surprise, since the muscle carnitine content (3–4 mM) represents approximately 98% of the total body stores and would presumably require large amounts of oral carnitine to further increase the endogenous store. Furthermore, the bioavailability of oral carnitine supplements is considered to be ~5 to 10% (Harper et al., 1988; Segre et al., 1988). As previously mentioned, there are virtually no studies that have examined the isolated effects of carnitine supplementation on weight loss. Therefore, evidence for enhancement of FFA oxidation following carnitine supplementation must come from exercise

studies. Although there have been reports of a decrease in the respiratory quotient (Gorostiaga et al., 1988) and lactate production (Siliprandi et al., 1990) during aerobic exercise following carnitine supplementation, the majority of human studies has not demonstrated an increase in lipid oxidation (Colombani et al., 1995; Decombaz et al., 1993; Marconi et al., 1985; Oyono-Enguelle et al., 1988; Soop et al., 1988; Vukovich et al., 1994). Therefore, without proof of increased muscle carnitine content following supplementation, or evidence of enhanced lipid oxidation, the use of carnitine as a weight loss supplement is not justified.

CONJUGATED LINOLEIC ACID

Conjugated linoleic acid (CLA) is an acronym for a group of geometric and positional isomers of linoleic acid (*cis*-9, *cis*-12-18:2). These include *cis*-9, *trans*-11-18:2 (the most abundant naturally occurring CLA), and at least seven other isomers of relatively low natural abundance. The primary dietary sources of CLA are animal based products (dairy products, average CLA content of 7.0 mg/g fat; beef, average CLA content of 5.5 mg/g fat), with minor contributions from vegetable sources (average content, 0.5 mg/g fat). Over the past decade, an abundance of scientific literature pertaining to the potential anticarcinogenic (Ha et al., 1987; Ha et al., 1990; Ip et al., 1991) and antiatherosclerotic (for review, see Rudel, 1999) properties of CLA has appeared. In the past few years, additional research has focused on the potential weight loss properties of CLA.

The first study to directly examine the effects of CLA on body composition was by Park and colleagues (1997). Weanling mice fed CLA-supplemented diets (0.5% CLA) for 28 days maintained similar body mass compared to the control group but significantly reduced body fat by 57 to 60% and increased body protein 4 to 13%. These results were not attributable to decreased food intake. However, specific alterations in both adipocyte and muscle metabolism were noted by the investigators, which may have accounted for the reduced body fat. In skeletal muscle, there was a significant elevation (54%) in total CPT activity in mice supplemented with 0.5% CLA for 7 days. Interestingly, this effect was only observed if mice were fasted overnight following the 7 days of supplementation. Unfortunately, CPT activity was determined in mixed hindlimb muscle, making it impossible to determine whether there were fibre-specific effects in terms of CLA's effects.

West and colleagues (1998) have documented a significant lowering of the nocturnal respiratory quotient following CLA supplementation, supporting the hypothesis that CLA enhances lipid metabolism in skeletal muscle. In addition, adipocyte metabolism is also altered by CLA. Adipocytes from CLA-treated mice (Park et al., 1997) demonstrated enhanced CPT activity, but unlike skeletal muscle, this effect was most pronounced in the group that was not fasted. Furthermore, adipocytes cultured in media containing CLA similar in concentration to that seen in the serum of treated mice (~70 μM) demonstrated reduced LPL activity. In addition, there is evidence that CLA inhibits both proliferation and differentiation of preadipocytes (Brodie et al., 1999; Satory and Smith 1999). Overall, this suggests that CLA directs lipids away from storage in adipose tissue and toward utilization in skeletal muscle. Unfortunately, the effects of CLA on muscle LPL activity have not been investigated. Since the original study by Park and colleagues (1997), several rodent studies have demonstrated weight loss and antidiabetic properties

Table 1 Summary of Body Composition Changes in Mice Induced by CLA

Investigator	Species	Approx. duration	Diet	Comments	Effects of CLA
(Park et al., 1997)	weaning mice	4 wks	5.5% corn oil +/– 0.5% CLA	Don't identify CLA mixture	↓ body fat 60% no change in energy intake
(West et al., 1998)	weanling mice	6 wks	15 vs. 45% fat +/– 1% CLA	39% *c* –9, *t* –11 41% *t* –10, *c* –12	↓ weight gain 50% in both groups ↓ body fat 43 to 80%
(Houseknecht et al., 1998)	obese vs. lean Zucker rats	2 wks	4% corn oil with 1.5% lard +/– 0.5% CLA	42% *c* –9, *t* –11 44% *t* –10, *c* –12	normalization of plasma insulin, FFA; Improved insulin sensitivity
(Delany et al., 1999)	mice	6 wks	45% fat +/– 0.25, 0.5, 0.75 and 1.0% CLA	39% *c* –9, *t* –11 41% *t* –10, *c* –12	↓ body fat, and specifically, retroperitoneal pads no change in energy intake
(Park et al., 1999a)	mice	7 wks	5.5% corn oil +/– 0.5% CLA	41% *c* –9, *t* –11 45% *t* –10, *c* –12	↓ body fat 50%

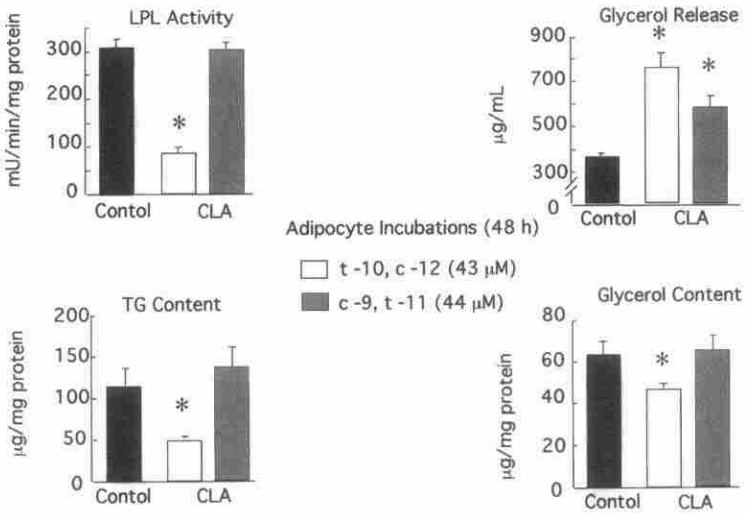

Figure 6. Importance of different CLA isomers in regulating lipid metabolism in incubated adipocytes. LPL, lipoprotein lipase; CLA, conjugated linoleic acid. *significantly different from controls. Modified from Park et al. (1999). **Lipids** 34: 235.

of CLA supplementation (Delany et al., 1999; Houseknecht et al., 1998; Park et al., 1999a; West et al., 1998; Table 1).

It is important to note that the CLA mixture utilized in above mentioned experiments is synthetically prepared and is comprised almost entirely of the *cis*-9, *trans*-11, and *trans*-10, *cis*-12 isomers in equal proportions. This clearly raises the question as to which CLA isomer is of biological significance. This was addressed in two subsequent studies by Park and colleagues, which clearly demonstrated that inhibition of body weight gain (Park et al., 1999a; Park et al., 1999b) and potentiation of lipolysis in adipocytes (Park et al., 1999b) were induced by the *trans*-10, *cis*-12 isomer (Figure 6). This is of considerable practical importance, since the apparently more biologically active form of CLA (in terms of weight loss and related metabolic effects) is not an abundant naturally occurring isoform. This raises the issue of whether naturally occurring CLA, as found in beef and dairy products, is of value in treating obesity. Furthermore, it will be important for manufacturers of commercially available CLA supplements to define the relative abundance of the various isomers in their product.

Thus, the information to date indicates that the *trans*-10, *cis*-12 isomer of CLA has potent stimulatory effects on weight loss and lipid metabolism in mice. However, no information regarding weight loss effects in humans is currently available.

Supplements That Elevate Thermogenesis/Metabolic Rate

It has been speculated that an impaired thermogenesis and reduced activity of the sympathetic nervous system (SNS) may be significant factors in the etiology of obesity (Astrup, 1995; Peterson et al., 1988; Tataranni et al., 1997; Yoshida et al.,

1994). Since the discovery that various isoforms of the mitochondrial uncoupling protein (UCP 2 and 3) are present in significant quantities in human tissues, there has been considerable interest in whether a reduced tissue expression of these uncoupling proteins is related to the development of obesity. Uncoupling proteins (UCPs) are regulated by SNS activity and thermogenic agents ENRfu (Cortright et al., 1999; Cunningham and Nicholls, 1987; Gong et al., 1997; Mory et al., 1984; Nagase et al., 1996) as well as by hormonal factors such as triiodothyronine and leptin (Bianco et al., 1988; Branco, 1999.; Commins et al., 1999; Gomez-Ambrosi et al., 1999; Gong et al., 1997; Liu et al., 1998; Scarpace et al., 1997; Zhou et al., 1997) and may represent a potential pharmaceutical target in the treatment of obesity. Gene expression (mRNA) of the ubiquitous UCP 2 has been shown to be reduced in adipose tissue of obese humans (Oberkofler et al., 1998) and is negatively correlated to the body mass index (BMI) in obese Pima Indians (Schrauwen et al., 1999). However, in skeletal muscle, expression of UCP 3 has been reported to be either unchanged (Nordfors et al., 1998; Vidal-Puig et al., 1999) or elevated in the muscle of obese humans (Bao et al., 1998), as has UCP 2 (Simoneau et al., 1998), creating controversy regarding the role of UCPs in obesity.

Regardless of the role of UCPs in the etiology of obesity, the apparent success of various sympathomimetic agents (ephedrine, amphetamines) used in the treatment of obesity in both human and animal models strongly implicates an impairment of SNS activity/thermogenesis in the development of obesity. In particular, the combination of ephedrine, caffeine, and aspirin (the "stack"), appears to have a potent stimulatory effect on dietary induced thermogenesis and is often used in weight loss remedies. In addition to the "stack," pyruvate has become very popular in the past several years as a supplementary adjunct to weight loss programs. Pyruvate is claimed to "accelerate the metabolic rate at the cellular level" and increase caloric expenditure. Interestingly, pyruvate is also claimed to be a performance enhancing agent, although the proposed mechanisms behind its ergogenic effect appear to have little in common with a potential weight loss effect.

EPHEDRINE

Ephedrine is derived naturally from the plant species Ephedraceae, including the Chinese Ma Huang herb. These plants produce a variety of ephedrine-type alkaloids, including ephedrine, pseudoephedrine, norephedrine, norpseudoephedrine, N-methylephedrine, and N-methylpseudo-ephedrine. Ephedrine is structurally similar to amphetamines and, due to its general sympathomimetic effects, can potentially increase lipolysis and thermogenesis (stimulation of postsynaptic β receptors), stimulate the release of norepinephrine (NE) through presynaptic $\beta 2$ receptors, as well as to induce vasoconstriction and elevation of heart rate (stimulation of α and $\beta 1$ receptors, respectively).

Although the role of reduced SNS activity in obese humans remains unclear (Peterson et al., 1988), it has been demonstrated recently that Pima Indians, who demonstrate a very high prevalence of obesity, have lower urinary NE concentrations, which correlate negatively ($r = -.38$; $p = 0.009$) with weight gain (Tataranni et al., 1997). Weight loss has been shown to be positively correlated ($r = 0.34$; $p = 0.05$) to urinary NE levels (Astrup, 1995), as well as basal metabolic rate ($r = 0.36$; $p < .001$; Yoshida et al., 1994). Thermogenic response to agents such as caffeine

have also been demonstrated to be highly correlated to subsequent weight loss during a program of caloric restriction and exercise (Yoshida et al., 1994), again implicating the role of the SNS in managing body weight. Thus, it is thought that ephedrine's thermogenic effects are primarily due to its stimulatory effect on the SNS. There is also evidence that ephedrine increases metabolic rate selectively through an increase in lipid oxidation (Astrup et al., 1992b).

The addition of aspirin (inhibition of prostaglandin synthesis) and methylxanthines (adenosine antagonism) interferes with the normal negative feedback of NE on its own presynaptic release fu (Krieger et al., 1990), leading to a further increase in synaptic NE concentrations (Figure 7). In rodents, the thermogenic effect induced by ephedrine and caffeine can be eliminated or reduced following sympathectomy and administration of adenosine analogues (Dulloo et al., 1991). Enhancement of the thermogenic response to food following ephedrine/methylxanthine/aspirin administration has been demonstrated in both lean (Horton and Geissler 1991) and obese individuals (Dulloo and Miller, 1986). Numerous human studies have reported significant weight loss with ephedrine supplementation, both alone (Astrup et al., 1985; Dulloo and Miller 1987; Pasquali et al., 1987) and in combination with caffeine and/or aspirin (Astrup et al., 1992a; Astrup et al., 1992b; Daly et al., 1993; Dulloo and Miller, 1987; Krieger et al., 1990; Toubro et al., 1993). However, at least two studies have failed to document enhancement of weight loss with ephedrine alone (Astrup et al., 1992a; Toubro et al., 1993) and several have clearly demonstrated enhanced weight loss when ephedrine is supplemented with caffeine and/or aspirin (Astrup et al., 1992a; Dulloo and Miller, 1987; Toubro et al., 1993). Reports of weight loss in humans due to caffeine alone have been equivocal (Astrup et al., 1992a; Toubro et al., 1993; Yoshida et al., 1994), while no studies have documented weight loss due to aspirin. Thus, the data from

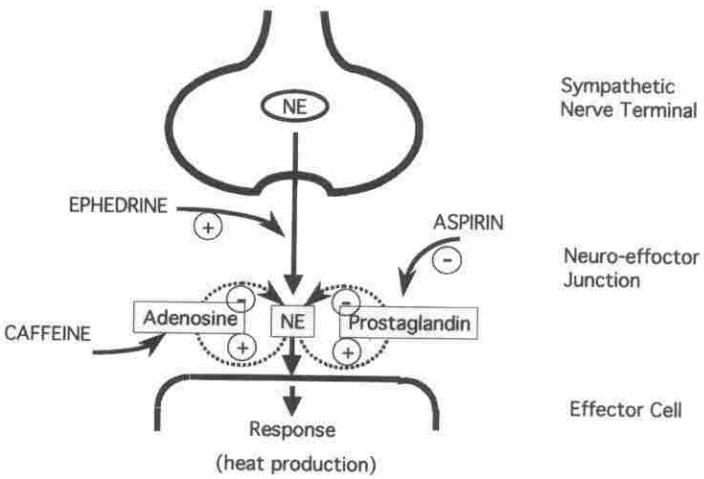

Figure 7. Schematic representation of the hypothetical mechanisms of potentiation by caffeine and aspirin of the thermogenic effects of ephedrine. (+), stimulation; (-), inhibition; NE, norepinephrine. Modified from Dulloo and Miller (1989). **Nutrition** 5: 4.

human studies support the hypothesis that caffeine and/or aspirin potentiate the weight loss effects of ephedrine. In isolation, ephedrine is generally less effective, and caffeine and aspirin do not appear to have any significant independent effects on weight loss.

In the human studies conducted to date, there is considerable variation in terms of types of subjects utilized, dosages of ephedrine/caffeine/aspirin given, duration of supplementation, and whether or not dietary intake was also restricted. Nevertheless, weight loss induced by ephedrine treatment consistently ranges from 0.6 to 0.9 kg/month (Astrup et al., 1992a; Astrup et al., 1992b; Daly et al., 1993; Krieger et al., 1990; Pasquali et al., 1987; Toubro et al., 1993), indicating that ephedrine's weight loss effects are not merely limited to obese individuals or to conditions where caloric intake is already restricted. Indeed, it may be true that the greatest potential abuse of ephedrine comes not from obese individuals but rather from athletes attempting to lose weight in order to either enhance performance or to drop to a lower competitive weight class. There are several anecdotal reports of death due to the overdose of ephedrine. Modest dosages of ephedrine, as used in scientific studies, appear to have only transient effects on blood pressure and heart rate (Astrup et al., 1992a; Robertson et al., 1981) while sustaining weight loss. However, the effects of long term use of ephedrine, both in terms of unwanted side effects and maintenance of weight loss, have not been established.

PYRUVATE

Over the past several years, one of the more popular nutritional supplements to be promoted as an effective weight loss product has been pyruvate. Pyruvate is a three carbon metabolite of glycolysis. The first demonstrated metabolic effect of pyruvate, and another triose, dihydroxyacetone, was a reduction in the development of fatty liver in rats receiving chronic ethanol feedings DIN ENRfu (Goheen et al., 1981; Stanko et al., 1978). It was hypothesized that by oxidizing the NADH generated from ethanol metabolism, pyruvate prevented the stimulation of triacylglycerol synthesis, which requires NADH as a cofactor. However, Stanko and colleagues (1978) also noted a decrease in abdominal fat, suggesting that the metabolic effects of pyruvate were not limited to merely oxidizing NADH and decreasing lipogenesis.

Subsequent studies demonstrated that inclusion of pyruvate and dihydroxyacetone in the diets of rats (Cortez et al., 1991; Stanko and Adibi, 1986) and pigs (Stanko et al., 1989) resulted in reduced weight gain and carcass fat, an increase in the metabolic rate (elevated O_2 consumption), and a shift toward lipid oxidation (decrease in respiratory quotient). The mechanism for increasing metabolic rate and lipid oxidation is unknown but may have been the result of an increase in plasma thyroxine and decrease in insulin Rfu (Stanko and Adibi, 1986).

In humans, several studies have demonstrated that high dosages of pyruvate and dihydroxyacetone may improve weight and fat loss (Stanko and Arch, 1996). Total dosage of trioses used in these studies ranged from 22 to 90 g, and the actual amount of pyruvate varied from 15 to 53 g. However, two of these studies (Stanko and Arch, 1996; Stanko et al., 1992) utilized morbidly obese women who were confined to bed rest in a metabolic ward and consumed only 500 to 1,000 kcal/d. In each study, women receiving trioses for 21 days lost 0.9 to 1.6 kg more body

weight and 0.8 to 1.3 kg more body fat than those receiving placebo. These findings have been criticized on the grounds that the conditions (morbid obesity, bed confinement, extreme caloric deficit) are so unique that they are of little relevance to the majority of the population attempting to lose weight (Sukala, 1998). Furthermore, the losses of body weight and fat reported in these studies (0.8 to 1.6 kg) are relatively small and are actually less than the losses induced by caloric restriction alone in the placebo group (Clarkson, 1998; Sukala 1998). However, in fairness it must be pointed out that the weight losses induced by pyruvate supplementation are similar to those reported in studies using ephedrine in combination with methylxanthines and aspirin (see above). More recent studies have also examined the effects of lower dosages of isolated pyruvate on weight loss (Kalman et al., 1998; Stone et al., 1999), but the results have been equivocal.

One of the major difficulties in interpreting and evaluating the aforementioned pyruvate studies is the glaring lack of a postulated, feasible mechanism to stimulate metabolic rate and induce weight loss. No evidence of hormonal alterations has been demonstrated in humans. It has been postulated that increases in muscle pyruvate may accelerate futile cycling between pyruvate and phosphoenolpyruvate and thereby increase energy expenditure. However, there is absolutely no evidence that pyruvate in the dosages administered in these studies even becomes elevated in the systemic circulation in order to subsequently elevate muscle pyruvate content. In fact, we have recently completed a study (Morrison et al., in press) demonstrating that acute, modest dosages of pyruvate (7 to 25 g) fail to elevate blood pyruvate over a subsequent 4-hr period (Figure 8). This may either be due to poor absorption, as suggested by the appearance of gastrointestinal distress,

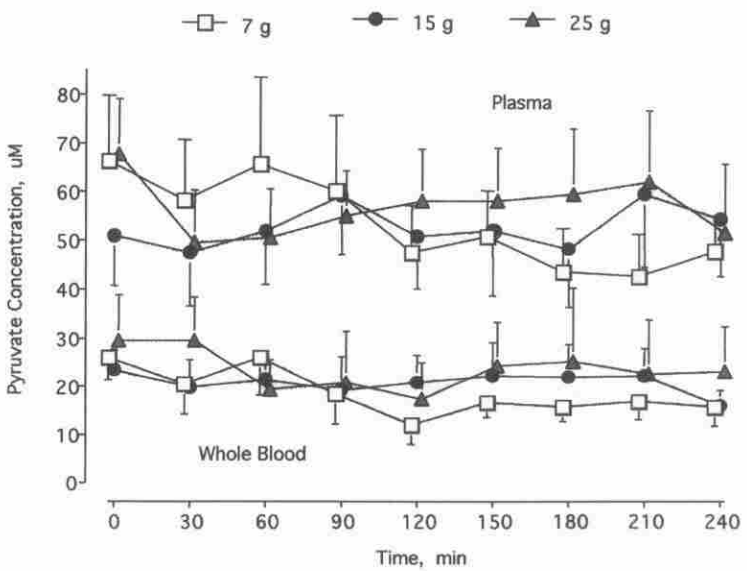

Figure 8. Whole-blood and plasma pyruvate concentrations after acute, oral ingestion of 7, 15, or 25 g of calcium pyruvate. Morrison et al. (2000). **J. Appl. Physiol.** 89:549-556.

or due to rapid clearance by other tissues such as the liver and muscle. A recent study (Constantin-Teodosiu et al., 1999), however, has clearly shown that direct infusion of high concentrations of pyruvate into the venous circulation fails to significantly alter muscle pyruvate content or TCA pool size. Finally, body composition in all human studies reported to date have used bioelectric impedance, which may not be appropriate for determining relatively small changes in body fat in the obese population (Kushner et al., 1996).

Although the use of high dosages of pyruvate and dihydroxyacetone has been shown to significantly enhance weight and fat loss in rodents and humans, the beneficial effects of low dosages of isolated pyruvate have not been established. This is of considerable practical significance, since pyruvate is marketed in 500 mg or 1 g capsules and does not contain dihydroxyacetone. Changes in body composition have been determined by bioelectric impedance, which may not be accurate. Furthermore, there is no clear mechanism by which pyruvate would increase metabolic rate. Recent studies have failed to demonstrate increases in blood pyruvate following supplementation or muscle pyruvate following venous infusion.

Supplements Purported to Inhibit Lipogenesis

The concept of nutrient balance is based on the premise that each macronutrient is metabolized (oxidized or stored) within its own compartment (Jequier and Tappy, 1999). The contribution of CHO or protein conversion into lipid (hepatic de novo lipogenesis) has been questioned in terms of its quantitative significance (Hellerstein et al., 1991a; Hellerstein et al., 1991b). It has been estimated that with CHO overfeeding, hepatic de novo lipogenesis ranges between 5 to 12 g per day (Aarsland et al., 1997; Schwarz et al., 1995). However, the long term consequences to such a process are considered, then the synthesis of 10 g of lipid per day would represent 32,850 kcal per year, or 4.1 kg (9.4 lb) of fat. As previously mentioned, early studies in rats receiving chronic ethanol feedings demonstrated that pyruvate decreases liver triacylglycerol accumulation, presumably due to its ability to oxidize NADH (Goheen et al., 1981; Stanko et al., 1978). In addition to pyruvate, hydroxycitrate is reported to inhibit lipogenesis in rodents.

HYDROXYCITRATE

Hydroxycitric acid (HCA) is the active ingredient of the native Indian plants, *Garcinia cambogia* and *Garcinia indica*. As of 1998, HCA has been incorporated in at least 14 different weight loss products sold across North America (Hobbs, 1994). Hydroxycitrate has been demonstrated to be a powerful in vitro inhibitor of ATP-citrate lyase (Watson et al., 1969; Watson and Lowenstein, 1970), which catalyzes the extramitochondrial cleavage of citrate to acetyl CoA and oxaloacetate, and represents the rate-limiting reaction in the de novo synthesis of long chain fatty acids.

Inhibition of hepatic lipogenesis in vivo and in liver supernatants from rats receiving a lipogenic diet (70% glucose) was reported by Sullivan and colleagues fu (1972). In vivo lipogenesis, monitored by conversion of ^{14}C-alanine into liver triacylglycerol, was reduced approximately 4-fold following an oral dosage of HCA

30 min prior to the lipogenic meal. Similar results were obtained if the HCA was consumed 1 hr prior to receiving the meal. However, if the HCA was taken either at the same time as the meal or more than 1 hr prior to the meal, the effect was significantly diminished (Figure 9A). A dose-response analysis revealed that HCA dosages of greater than 2.6 mmol/kg body weight were the most effective at suppressing lipogenesis (Figure 9B). These findings were confirmed by a follow-up study by Sullivan and colleagues (1974) as well as by Lowenstein (1971). However, Lowenstein observed that significant reductions in lipogenesis, monitored by the incorporation of $^{3}H_{2}O$ into liver triacylglycerol, was significantly depressed following a high-CHO meal with 0.4 mmol/kg body weight of HCA. Ketone production in isolated perfused rat liver has also been demonstrated to be depressed with 2 mM HCA (Brunengraber and Lowenstein, 1976).

Prior to 1998, only two peer-reviewed publications had been published examining the effects of oral HCA supplementation on body composition and weight loss in humans (Conte, 1993; Girola et al., 1996). Each of these studies reported enhanced weight loss in subjects receiving HCA for a 4 to 8 week period. However, in each study, HCA supplementation was accompanied by either a low fat diet or chromium and chitosan supplementation, making a valid assessment of HCA's isolated effects on weight loss impossible. In addition, one study (Conte, 1993) did not utilize statistics as part of their analysis, and the other only utilized very low dosages (55 mg/d, or 0.004 mmol/kg) of HCA (Girola et al., 1996). Heymsfield and colleagues (1998) examined the effects of higher oral dosages of HCA (1500 mg/d; equivalent to ~ 0.1 mmol/kg). Overweight men and women were treated with either HCA or placebo for 12 weeks while following a high-fibre, low energy diet. Body weight and fat loss (determined by DEXA), was actually slightly greater in the placebo group, although the differences were not statistically significant (Figure 10).

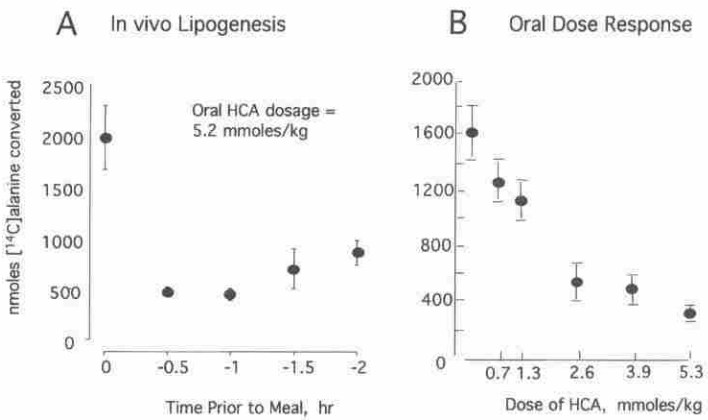

Figure 9. Inhibition of hepatic lipogenesis in rats following an acute dosage of HCA. (A) Effect of timing of HCA dosage prior to a lipogenic meal; (B) Effect of various HCA dosages on hepatic lipogenesis. HCA, hydroxycitrate. Modified from Sullivan et al. (1972). **Arch. Biochem. Biophys.** 150: 183.

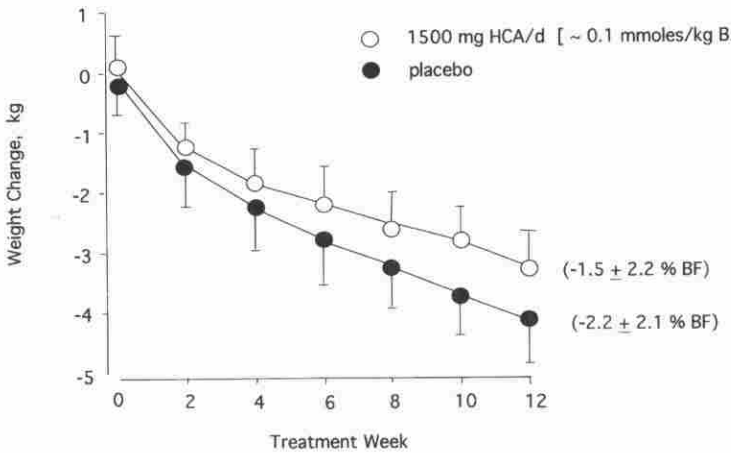

Figure 10. Effect of oral hydroxycitrate supplementation on weight loss in overweight individuals on a restricted caloric diet. HCA, hydroxycitrate; B.W., body weight; B.F., body fat. Modified from Heymsfield et al. (1998). **JAMA** 280(18): 1598.

Thus, the documented effects of very high dosages of HCA in vitro or in vivo lipogenesis in rats following lipogenic meals appears to be unequivocal. According to these studies, HCA should be consumed between 30 and 60 min prior to a meal for maximal effect. However, few human studies have been published and all have utilized HCA dosages much lower than those given in animal studies. No significant effects on body weight or composition attributable to modest, isolated dosages of HCA have been documented. Interestingly, and in parallel to the human studies that have examined the weight loss effects of pyruvate, no studies have actually measured blood or tissue levels of HCA in response to supplementation to determine the efficacy of various dosages.

Summary

Although there remains considerable debate regarding the role of macronutrient balance in the etiology of obesity, the consumption of high-fat diets appears to be strongly implicated in its development. Considerable evidence in rodents and humans has accumulated demonstrating an impaired capacity to oxidize lipids in the obese or obese-prone condition. Furthermore, the inability to rapidly adjust lipid oxidation to equal dietary fat intake suggests that individuals attempting to lose body fat would be well advised to curtail their fat consumption. Nevertheless, several current fad diets recommend drastically reduced CHO intake, with the underlying assumption that by reducing circulating insulin levels, lipolysis and lipid oxidation will be enhanced and fat storage reduced. Modest consumption of CHO (~50% kcal), particularly in inactive individuals, may help in this regard. Although numerous supplements are marketed to increase fat loss, few are actually supported by scientific studies. Several have only been proven to be effective at high dosages or only in rodents. The effects of ephedrine, in conjunction with methylxanthines and aspirin, in humans appears unequivocal, but may cause vari-

ous cardiovascular side effects and can potentially be abused with catastrophic results. Conjugated linoleic acid, based on the results from animals studies, appears very promising and warrants human experimentation.

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