Dear Sir:

Consumption of green tea may enhance health because it reduces the incidence of cancer in various experimental models, is a potent antioxidant, and modulates serum cholesterol concentrations (1). Green tea also has effects on body weight (2, 3) and energy expenditure (4). Dulloo et al (4) reported that 24-h energy expenditure (EE) and fat oxidation increased in healthy, young men who consumed a green tea extract containing caffeine and green tea polyphenols. Because a dose of caffeine equivalent to that found in the green tea extract did not affect 24-h EE, it was concluded that green tea polyphenols, especially the most abundant one—epigallocatechin gallate (EGCG)—may stimulate thermogenesis and fat oxidation. Experimental analysis of the mechanisms by which green tea exerts its effect is difficult because green tea is a complex mixture of various phytochemicals (1) that may not be absorbed easily from the gastrointestinal tract (5). A synergistic effect of EGCG and caffeine may be responsible for enhancing thermogenesis and fat oxidation, although this was not investigated in the study by Dulloo et al.

The effects of green tea extracts on EE and fat oxidation observed in the study by Dulloo et al (4) are in contrast with the findings of our studies, in which we showed that intraperitoneal injection of EGCG (>98% pure), but not other structurally related catechins—such as epicatechin (EC), epigallocatechin (EGC), and epicatechin gallate (ECG)—caused acute body weight loss in male and female Sprague-Dawley rats within 2–7 d of treatment (2, 3). EGCG also significantly reduced or prevented an increase in body weight in lean (Figure 1A) and obese (Figure 1B) male (3) and female Zucker rats. The effective dose of EGCG was initially ~30–50 mg EGCG/kg body wt. However, these rats gradually adapted within 1 wk and higher doses of EGCG (=100 mg/kg body wt) were needed to reduce or prevent increases in body weight. The loss in body weight was reversible; when EGCG administration was stopped, animals regained the lost body weight (Figure 1A). Lean and obese male Zucker rats injected intraperitoneally with 70–90 mg EGCG·kg body wt−1·d−1 lost 10–13% of their body weight relative to their initial weight and 25% of their body weight relative to the control after 8 d of treatment.

The weight-loss effect of EGCG in rats may have been due to a reduction in food intake (3). Male Sprague-Dawley rats, given EGCG orally, consumed ~15% less food than did the control rats and lost 5% of their initial body weight. Male and female Sprague-Dawley rats and male lean and obese Zucker rats injected intraperitoneally with EGCG consumed ~50–60% less food than did control rats. This effect was catechin-specific; EGCG—but not EC, EGC, or ECG—resulted in a reduction in food intake in Sprague-Dawley rats. The effect of EGCG on food intake reduction (Figure 1, C and D) was independent of an intact leptin receptor because leptin receptor–intact lean Zucker rats and leptin receptor–defective obese Zucker rats (6) had similar responses to EGCG treatment (3). EGCG, therefore, may interact specifically with a component of the leptin receptor–independent appetite control pathway.

Dulloo et al (4) also observed that EGCG-containing green tea extracts were more potent than were equimolar concentrations of caffeine alone in stimulating in vitro the respiration rate of brown adipose tissue. Additionally, the in vitro thermogenic effect of a green tea extract on brown adipose tissue could be mimicked by EGCG. The enhanced rates of thermogenesis and respiration by green tea extracts may support our in vitro studies in which EGCG reduced the total triacylglycerol accumulation of murine 3T3-L1 preadipocytes during their differentiation to adipocytes. However, we found that EGCG also inhibited the proliferation of 3T3-L1 preadipocytes. The concentration of EGCG that inhibited proliferation by 50% was ~10 μmol/L; at this concentration, EGCG—but not EC, EGC, or ECG—inhibited insulin-induced increases in cell number (by 34%) and the triacylglycerol content (by 54%) during a 9-d period of differentiation. Recently, EGCG and ECG were shown to be inhibitors (50% inhibition at 0.31 mmol/L) of acetyl-CoA carboxylase activity, a rate-limiting step in the fatty acid biosynthesis pathway, in 3T3-L1 cells (7). EGCG at a dose of 10–100 μmol/L could also reduce the cell number and triacylglycerol content of differentiating preadipocytes treated with dexamethasone, 1-methyl-3-isobutylxanthine, and insulin. Therefore, the in vitro effect of EGCG on fat tissues may be mediated by modulation of hormone-stimulated cell proliferation and differentiation or by inhibition of fat cell functions.

The effects of long-term daily oral consumption of 2–4 cups (500–1000 mL) of green tea or EGCG-containing green tea extracts may mimic some of the acute effects of EGCG. Studies have shown that oral consumption of green tea, EGCG, or EGCG-containing green tea extract can lower serum and LDL cholesterol, increase HDL cholesterol, and lower serum glucose (1, 3, 8). On the basis of the in vivo effects of EGCG on body weight loss, body fat, serum lipid nutrients, thermogenesis, and fat oxidation (1–4, 8) and of the in vitro effects of EGCG on fat cell functions (4, 7), long-term consumption of green tea may decrease the incidence of obesity and, perhaps, green tea components such as EGCG may be useful for treating obesity. Recently, a weight-reducing effect of oolong tea (9) was observed in mice consuming a high-fat diet. It is possible that the EGCG in the oolong tea was responsible for the observed effects. Oolong tea, however, contains much less EGCG than does green tea, so it remains to be established what components of oolong tea caused
the weight reduction in these mice. Studies, like ours, with purified components are necessary to identify active components.

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Reply to Y-H Kao et al

Dear Sir:

I am grateful to Kao et al for their interesting compilation of recent data about the effects of epigallocatechin gallate (EGCG)—the most abundant catechin of green tea—on various variables in vitro and in vivo, which collectively underscore the potential antiobesity properties of this polyphenol. Nobody will disagree with their final remark that the use of purified components are necessary for identifying the active components that confer green tea (or any other phytoproduct) with potential antiobesity properties. In fact, as a follow-up to our in vivo study that indicated the ability of a green tea extract particularly rich in EGCG to stimulate thermogenesis in lean and overweight humans (1), we also investigated the effect of pure (–)-EGCG on tissue respiration rate in vitro. We showed its dependency on sympathetically released noradrenaline (NE) in the activation of peripheral thermogenesis (2). There is clearly a need for further studies investigating the effects of EGCG on long-term energy balance and substrate utilization in animal models and in humans. Toward this end, it is important to clarify and to explore some of the issues raised by Kao et al.

First and foremost, we feel that an important aspect of our studies pertaining to green tea and thermogenesis was missed by Kao et al: it is not EGCG alone, but the combination of EGCG and caffeine—via their interactions with sympathetically released NE—that confers green tea with its ability to enhance thermogenesis. Although this proposal is largely speculative, on the basis of our human studies measuring energy expenditure and urinary catecholamines (1), it is strongly supported by our in vitro studies in brown adipose tissue fragments, which indicate that EGCG is a rather weak stimulus of thermogenesis and that the thermogenic potency of green tea resides in a synergistic interaction between the 2 main pharmacologically active ingredients of green tea—EGCG and caffeine—and sympathetically released NE (2). The mechanisms behind these synergistic interactions are to be expected because EGCG and caffeine act in concert along different control points underlying NE-induced thermogenesis, namely that EGCG inhibits the enzyme catechol-O-methyltransferase that degrades NE within the synaptic cleft (3), whereas caffeine inhibits primarily the phosphodiesterase enzyme complex that...
degrades cyclic AMP, the intracellular secondary messenger for NE-mediated thermogenesis. The net result of the combination of EGCG and caffeine may, therefore, be a reduction in the effects of 2 brakes along the pathway of NE-activated thermogenesis. One would therefore expect the combination of EGCG and caffeine to be more effective than caffeine alone in potentiating thermogenesis under sympathetic neural control, such as in response to meals or to physical activity.

Second, the new data presented by Kao et al pertaining to the anorectic properties of injected EGCG in rats raise questions about the availability of this catechin to various tissues. At such high doses of EGCG—likely to be achievable only by injection, given the poor absorption of this catechin when taken orally—one wonders about the relevance of these suprapharmacologic doses vis-à-vis the effect of oral consumption of green tea on food intake. In our human studies, although conducted over only 1 d in a calorimeter, none of the subjects had a reduced food intake after green tea treatment or indicated that consumption of the green tea extract altered their “feeling of fullness.” These findings are in sharp contrast with the results of our previous study—also conducted over just 1 d in a calorimeter—that investigated the thermogenic properties of a combination of ephedrine, caffeine, and theophylline. In that study, postobese subjects had not only an 8% increase in 24-h energy expenditure but also a 16% decrease in 24-h energy intake (4). Although this “cocktail,” particularly one of its ingredients—ephedrine—is well known for its effects on the central nervous system, 2 intriguing questions arose from the animal studies reported above by Kao et al: are the observed anorectic effects after EGCG injection also centrally mediated and, if so, can EGCG or its metabolites cross the blood-brain barrier? Alternatively, could it be that when EGCG is administered long term, its appetite-suppressing effect is not direct, but via its effects in enhancing fat oxidation, which in our acute human study was much more impressive than was the increase in energy expenditure. According to the nutrient balance theory, the balance between fat oxidation and fat intake (unlike for carbohydrate and protein balances) is not precisely regulated and the failure to increase fat oxidation in response to excess fat intake will result in increased appetite and obesity. Consequently, EGCG, by promoting fat oxidation irrespective of whether it stimulates energy expenditure, could be of value in minimizing the tendency for hyperphagia associated with our typical high-fat, energy-dense diets.

Last, the current surge of interest in green tea and its potential role in the management of obesity must be put into the wider context of the interest by the public, media, and industry in functional foods, nutraceuticals, and many different so-called natural supplements (the supply and demand theory operating at its very best!). Green tea, which has high catechin and caffeine contents, is only the latest addition to an increasing list of dietary ingredients now known to be capable of stimulating thermogenesis and fat oxidation by interfering with the sympathoadrenal system. These include the capsaicinoid compounds, which confer pungency to spicy ingredients such as chilies, mustard, and red pepper; the methylxanthines (eg, caffeine) found in beverages such as coffee and tea; the medium-chain-triacylglycerols found in coconut oil, which is the main cooking oil in many parts of Asia and Africa; and the combination of catechins and caffeine found in green tea and consumed widely in China and Japan. They have all been shown to stimulate thermogenesis, fat oxidation, or both in humans in amounts compatible with their daily intake in the diet of specific communities (1, 6–10). One wonders, therefore, about the extent to which these ingredients, which are consumed in the diets of most cultures today, could already be helping many of us to burn excess dietary fat, but also as to what type of safety and efficacy standards to which they should be subjected before being advocated as supplements for the purpose of managing obesity.

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Accuracy of food-frequency questionnaires

Dear Sir:

In their recent article in the Journal, Schaefer et al (1) concluded that a food-frequency questionnaire developed by our group did not provide reliable estimates of absolute intakes of dietary fat or cholesterol. They based this conclusion on an extremely small evaluation of 19 subjects who were fed 3 different diets for 6-wk periods in a tightly controlled metabolic study.

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Although I agree that food-frequency questionnaires are not an optimal method for assessing group means in intervention trials (2), the conclusions reached by Schaefer et al are based on a highly artificial context distinctly different from that for which food-frequency questionnaires were designed. Because measurement of long-term dietary intake is the objective, this and most food-frequency questionnaires are based on average intakes of foods over the previous year. In this particular application, subjects were cycled through 3 different diets in addition to their customary diets for 6-wk periods. Thus, it is not surprising that there would be a blurring of dietary intakes assessed by the food-frequency questionnaire.

Second, the subjects were given all the foods that were to be eaten and thus did not participate in the selection, purchase, or preparation of foods, which would normally be the case when food-frequency questionnaires are used in epidemiologic studies. Furthermore, to obtain a contrast in diets in metabolic studies, recipes are typically altered from what participants might normally use. Allowing participants to see the menus does not at all replicate the usual involvement of subjects in determining, and thus developing a knowledge about, their long-term dietary patterns.

Schaefer et al suggested that the diet records provided more accurate information in their study, but they acknowledged that the results were artificial because the investigators knew the exact recipes to use for dishes that were reported (because they provided the food themselves). However, their experience illustrates one of the serious problems with diet records in that fewer than one-third of the subjects actually completed the records. In this contrived example, this made no difference because everyone was fed the same food. However, in a more realistic context, persons completing diet records are likely to have diets different from those who do not complete diet records, which could lead to a serious bias. Additionally, it was shown in many intervention trials using objective measures of dietary intake that individuals overreport compliance when they use diet records (2). This is likely to be the result of better compliance during recording of the diets than on other occasions. There appear to be similar biases for 24-h dietary recalls when individuals know that they will be interviewed about their previous day’s diet (3). Thus, the most unbiased measure of average group compliance in intervention studies appears to be neither food-frequency questionnaires nor diet records but rather “surprise” 24-h dietary recalls conducted on random days by telephone interview (2) or the use of biomarkers when possible.

Additional data on the validity of various dietary assessment methods would be useful, but the study design used by Schaefer et al could be highly misleading.

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REFERENCES

Reply to WC Willett

Dear Sir:

Food-frequency questionnaires are useful in ranking individual intakes to describe relations between diet and disease in large epidemiologic studies. The use of food-frequency questionnaires to estimate absolute nutrient intakes is frequent in research, although food-frequency questionnaires have not been validated against an appropriate standard (1–4). Validation of food-frequency questionnaires (comparison with an observed diet of chemically defined composition for 1 y) is not possible given the expense of such an undertaking and the difficulty in finding subjects to participate in such a study. Thus, we chose to investigate the efficacy of the food-frequency questionnaire during a controlled metabolic study in which biochemical evaluation (serum lipid profiles) was concurrent (5). We provided subjects with 3 diets composed of common and recognizable foods, but that varied greatly in diet composition, in 6-wk intervals. Triple samples of each diet were chemically analyzed to provide the most accurate standard by which to compare or validate food-frequency intake estimates. We then asked our subjects to report their dietary intakes by using the Willett food-frequency questionnaire at the end of each 6-wk period, with instructions to base responses according to their intake during this 6-wk period.

Willett pointed out that our methods were “artificial.” Although our methods did not simulate a free-living situation, we argue that in real life many persons consume meals in restaurants and do not know how foods are prepared. Furthermore, it is typical for one person in a family to be responsible for food preparation, whereas other members remain unaware of the meal preparation or type of ingredients used. Moreover, the reference standard for assessing the validity of any diet instrument must be, in our view, a chemically defined diet. Such an assessment has never been carried out by Willett with his instrument.

Willett also pointed out that subjects were provided all of their food, and that this does not replicate a subject’s usual involvement in developing knowledge of his or her long-term dietary pattern. We were not asking individuals to report their long-term dietary intakes, but rather to report on the diet that they were consuming over the previous few weeks. Finally, our subjects were not blinded to the study phase and were aware of the fat content being altered in each phase of the study. They were aware that items were reduced in total fat but were unaware of the types of fats used in cooking. Because the subjects were given their food, this should have been a best-case scenario for the food-frequency questionnaire. We know of no more valid method than assessing an instrument in comparison with a chemically defined diet.

We agree that dietary assessment tools, whether they involve food-frequency questionnaires or food diaries, are subject to reporting biases. In our study, however, the blood lipid profiles of the subjects were consistent with their actual dietary intakes and were accurately assessed by 3-d food records. Our subjects may have been free of bias in their reporting because they were
given all of their food during the study and their body weight and blood lipids reflected compliance with the diets provided. Our subjects had no reason to falsely report their dietary intakes.

We agree that the subjects were asked to report on their dietary intake over a 6-wk period as opposed to a 1-y period, which is the recommended time for using the food-frequency questionnaire. We also agree that our sample was small (19 subjects), but we believe that studying few subjects carefully is more valuable than is studying many subjects with a nonficcacious instrument. Our findings indicate that food-frequency questionnaires do not accurately estimate absolute dietary intakes. We found that our 3 diets, composed of very different amounts of total fat (15%, 26%, and 35% of energy), were estimated to be very similar by the food-frequency questionnaire (22%, 27%, and 28%, respectively, of energy). The food-frequency questionnaire could not reliably distinguish a high-fat diet from a low-fat diet in our study. Our data are consistent with the view that 3-d food records provide a much more accurate assessment of dietary macronutrient intake than do food-frequency questionnaires, which in our view can be highly misleading.

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REFERENCES

Where is the glutamine? Intradialytic supplementation may not solve all issues in amino acid balance

Dear Sir:

Glutamine is the most abundant amino acid in intra- and extracellular fluid, although the total amount of glutamine in the skeletal muscle pool was recently downwardly revised (1). Our interest in the nutrition and metabolism of this amino acid pro-

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Reply to NW Solomons et al

Dear Sir:

We thank Solomons et al for their interest in our study on amino acid losses during hemodialysis with polyacrylonitrile membranes and the effect of intradialytic amino acid supplementation (1). We are glad to have the opportunity to respond to the issues they raised.

First, glutamine is not contained in the amino acid solution. The composition of infused amino acid solution was shown in Table 2 of our article and, as the authors commented, glutamine was not included. The amino acid infusate used in our study was Aminoplasmal (Braun Medical, Barcelona, Spain). For the purposes of the investigation we used a solution easily available and widely used in clinical practice daily, instead of a specifically prepared amino acid solution, even though several of the nonessential amino acids (citrulline, glutamine, and taurine) were not contained in the preparation.

Second, even though citrulline, glutamine, and taurine were not contained in the amino acid solution, we decided to analyze the hourly losses and the plasma concentrations of these amino acids during the dialytic procedure (Tables 3 and 4). As is logical, and again in agreement with Solomons et al, because these amino acids were not administered during hemodialysis, their serum concentrations experienced the greater decrease during dialysis with supplementation, with no significant differences in the percentage of reduction with respect to dialysis without supplementation. Furthermore, and not surprisingly, citrulline, glutamine, and taurine are the only 3 amino acids that have no greater losses during dialysis with supplementation (Table 5).

Third, glutamine, unlike the essential amino acids that must be externally supplemented, is a nonessential amino acid that is synthesized by physiologic metabolic reactions from glutamic acid and ammonia. This amino acid was not included in Table 6 because that table depicted the net balance of individual amino acids during hemodialysis with amino acid supplementation. Glutamine, citrulline, and taurine were not included in Table 6 because the net balance of amino acids, as specified in the methods section, was calculated as (amino acid contained in the infusate) – (amino acid lost into dialysate with supplementation) – (amino acid lost into dialysate without supplementation). Therefore, the net balance of the amino acids not contained in the infusate could not be calculated.

Finally, we thank Solomons et al for their interesting comments on the solubility of glutamine dipeptides and their potential use in intradialytic amino acid supplementation.

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Amino acid losses during intradialytic parenteral nutrition

Dear Sir:

Navarro et al (1) reported recently on amino acid losses during hemodialysis therapy without and during concomitant infusion of amino acids as intradialytic parenteral nutrition. The obligatory basal loss of amino acids without simultaneous amino acid infusion was 12.5 g/4 h. When 25.7 g amino acids was infused during hemodialysis, losses increased to 28.3 g (15.8 g more), so the net retention rate of amino acids was only 25.7 – 15.8 = 9.9 g, which is 38% of the amount infused. (These are my calculations; the authors give slightly different numbers, ie, a net uptake of 10.6 g).

These results are in variance with the results of previous investigations in this field and contradict the physiology of amino acid metabolism. Obviously, there is a basal amino acid loss (averaging 2–3 g/h, as was also confirmed by Navarro et al) and—if amino acids are given during hemodialysis as nutritional support—an additional loss because of the elevation of plasma amino acid concentrations during infusion. However, Wolfson et al (2) showed clearly that an amino acid infusion during hemodialysis only marginally increases amino acid elimination. In their study, basal amino acid loss (without additional amino acid infusion) was 8.2 g. The total loss of amino acids when 39.5 g amino acids was given during hemodialysis increased to only 12.6 g (4.4 g more); thus, the net uptake of amino acids infused was 39.5 – 4.4 = 35.1 g, ie, 89%. Recently, these findings were confirmed for high-flux polysulfone membranes by Berneis et al (3), who evaluated amino acid losses during intradialytic parenteral nutrition (3). During 4 h of hemodialysis, 48 g amino acids was infused continuously, but total amino acid loss into the dialysate was only 10.9 g, so ≥77.3% of the amino acids infused was retained. (Basal amino acid losses was not measured, so the net retention must have been even higher.)
These results were also to be expected. The endogenous clearance of amino acids is much higher than is the exogenous, dialytic clearance. In hemodialysis patients, mean endogenous amino acid clearance is \( \approx 900 \text{ mL/min} \) (4). This means that an amino acid infusion at the dosage used by Navarro et al does not substantially increase plasma amino acid concentrations and thus can enhance amino acids losses during hemodialysis only moderately.

The only explanation for the excessive amino acid losses reported by Navarro et al is that amino acids were infused into the arterial line before the dialysis membrane, and this obviously is not appropriate.

Intradialytic parenteral nutrition has been shown to ameliorate several indicators of nutritional status, such as an increase in plasma protein concentrations, an increase in anthropometric variables, and an amelioration of immunocompetence (5). Nevertheless, it remains to be shown convincingly that this nutritional intervention can alter the course of disease and improve morbidity and mortality. One fact, however, is clear: the amino acids infused during hemodialysis are retained at a percentage of \( \geq 75\% \).

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REFERENCES


Reply to W Druml

Dear Sir:

We thank Druml for his interest in our study on amino acid losses during hemodialysis with polyacrylonitrile membranes and the effect of intradialytic amino acid supplementation (1) and are glad to have the opportunity to respond to the issues he raised.

The first discrepancy arises in the calculation of the net retention of amino acids. In our study, the mean net uptake of amino acids was 10.6 g; if the calculations of Druml are used, this uptake is 9.9 g. This slight difference may be explained by the fact that our calculations were based on the net balance of individual amino acids, not the total amounts.

Second, as mentioned by Druml, in the study by Wolfson et al (2) the basal losses of amino acids (without supplementation) were 8.2 g, which increased to 12.6 g after amino acid administration. This increase of 4.4 g in amino acid losses, which represents 53.6% of basal losses, may be considered at least as relevant, but not marginal. Concerning amino acid balance in our study, hemodialysis with infusion of 25.7 g amino acids resulted in a net uptake of 10.6 g, which represents 44% of amino acids infused. What is the reason for the differences between this and the results of previous studies by Wolfson et al (2) and Berneis et al (3)?

Several factors must be taken into account. First, in the study by Wolfson et al, patients received an infusion of 400 mL amino acids and 400 mL of 50% glucose (200 g d-glucose), whereas in the study by Berneis et al amino acids were administered with glucose (150 g) and a fat emulsion (50 g). On the contrary, an important characteristic of our study was that amino acids were supplemented without glucose or other nutrients to avoid these confounding factors. It is possible that the infusion of glucose or lipids favors the cellular uptake of amino acids and therefore can explain the higher positive balance of amino acids observed in these previous studies.

Second, the characteristics of the dialysis session are important. Several aspects may affect the losses of amino acids during this procedure, such as blood flow, dialysate flow, intake of food during the session, and weight loss. Finally, a critical factor in the dialytic treatment is the dialysis membrane. Wolfson et al. used a Travenol, Lundia, or Nova dialyzer; Berneis et al. used a polysulfon dialyzer; and we used a polycrylonitrile dialyzer. The classic and most commonly used membrane for hemodialysis is cuprophane, but new synthetic membranes such as polysulfone, polycrylonitrile, and polymethylmethacrylate have become available during the past decades. Despite these membranes being considered as highly biocompatible, their characteristics depend on the specific membrane, not on class. Therefore, the amino acid losses need to be evaluated for each individual membrane because the membranes’ intrinsic properties (eg, polarity, capacity for capture of amino acids, physicochemical characteristics, and bulk charges within the membrane) may modify important aspects of the dialytic procedure, including losses of amino acids and other nutrients.

Third, as is obvious, the amino acids were infused into the venous line after the dialyzer. Druml commented that amino acid infusion at a dosage such as that used by us would not substantially increase plasma amino acid concentrations. This conclusion is evident from Table 4 in our article. The table shows that dialysis with amino acid infusion results in a significant increase in the serum concentration of only 5 amino acids (leucine, asparagine, citrulline, cystine, and taurine) compared with basal values, whereas the plasma concentration of the other amino acids did not change significantly. This statement is specified in the discussion; furthermore, we highlighted that amino acid administration in our study prevented the reduction in the plasma amino acids observed after the dialytic procedure, with no significant modifications in the plasma concentrations of essential, nonessential, branched-chain, and total amino acids. Moreover, on the basis of these results, we hypothesized that an increase in the initial dosage of amino.
acids administered might result in a significant rise in plasma amino acid concentrations.

Finally, we agree with Druml that nutritional intervention can alter the course of disease in dialysis patients, with an improvement of morbidity and mortality. However, there are currently no studies designed to investigate the effect of different schedules of amino acid supplementation on the outcome of dialysis patients. Therefore, there is no evidence about the percentage of amino acids that must be retained after supplementation to achieve any beneficial effect. Thus, the value suggested by Druml (≥75%) is arbitrary.

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REFERENCES


Fat and carbohydrate balances during adaptation to a high-fat diet

Dear Sir:

During consumption of a diet that meets energy requirements, it takes several days before fat oxidation adapts to fat intake when the diet composition is changed from low fat to high fat (1). This finding was confirmed recently by the results of a study by Smith et al (2), who showed a delay in the rise in fat oxidation when the dietary fat content was shifted from 37% to 50% of energy. Smith et al noted that there was a striking degree of variability in the rate of adaptation of fat oxidation to this increased fat intake. According to their data, postabsorptive respiratory quotient, fasting insulin, and maximal oxygen uptake (VO2max) were predictors of the capacity to adapt fat oxidation to fat intake.

Although we agree with the conclusion of Smith et al that there is high variability in the capacity to adapt fat oxidation to fat intake, we believe that these data should be interpreted with caution. It is known that there is a clear hierarchy in the maintenance of macronutrient balances, with carbohydrate and protein balance having the highest priority (3). Fat oxidation, on the other hand, is determined mainly by the difference between energy expenditure and carbohydrate and protein oxidation. Therefore, fat balance is strongly correlated with energy balance. This is where we believe caution should be taken with the interpretation of the data of Smith et al.

In Smith et al’s study, the cumulative fat balance over 4 d, when subjects were consuming a high-fat diet in a respiration chamber, was considered to be a good indicator of the capacity to adapt fat oxidation to fat intake. However, because energy balance and fat balance are strongly correlated, the cumulative fat balance over 4 d might just reflect the cumulative energy balance. Although Smith et al proposed to feed the subjects in energy balance, energy balance was not reached on any of the days in the respiration chamber. More important, there was great interindividual variation in the magnitude of energy balance (SEM: 500 kJ/d; n = 6). The interindividual variation in fat balance might also reflect the interindividual variation in energy balance. In this respect, it is important to note that in the study by Smith et al, subjects’ energy requirements were calculated by multiplying resting metabolic rate by a physical activity index (PAI) factor of 1.5. However, on average, a PAI factor of 1.4 was achieved in the respiration chamber, resulting in positive energy balance. It is known that physical fitness (as could be indicated by VO2max) is related to the PAI, ie, the fitter subjects are more active throughout the day (4). This means that subjects with higher VO2max values might have been more active in the respiration chamber (higher PAI) and consequently have showed a less positive energy balance and thus a less positive cumulative fat balance. Thus, the correlation between VO2max and cumulative fat balance might be artificial. The same reasoning might hold for fasting insulin concentrations because physical fitness improves insulin sensitivity (5). It is very likely that, in this situation, energy balance determined the rate of adaptation of fat oxidation to the high fat intake. A situation of zero energy balance should be achieved before conclusions can be made about interindividual variation in the capacity to adapt to high-fat diets.

Second, we believe that the role of glycogen stores cannot be neglected in the interpretation of the data. In his 2-compartment model, Flatt (6) showed that one can adapt fat oxidation to an increased fat intake by 2 mechanisms: 1) expansion of the fat stores or 2) maintenance of the glycogen stores in a lower range. In the short term, and with subjects in (near) energy balance, the first mechanism is of no importance in the adaptation of fat oxidation to fat intake. We showed previously that glycogen stores are indeed important in the rate at which fat oxidation is adapted to a high fat intake (1, 7, 8). Because fat oxidation does not adapt rapidly to the increased fat intake with a high-fat diet, subjects will be in negative carbohydrate balance during the first days of the high-fat diet. This means that they will ultimately lower their glycogen stores, which allows, according to Flatt’s model, fat oxidation to increase. Indeed, fat oxidation matched fat intake after several days of consumption of a high-fat diet (1). When glycogen stores were lowered acutely before the start of the experiment, however, both lean and obese subjects were capable of adjusting fat oxidation to a high fat intake within 1 d (7, 8). Because the subjects in the study by Smith et al were in positive energy balance, they probably did not reduce their glycogen stores sufficiently to allow fat oxidation to completely adapt to fat intake. Again, the degree of positive energy balance might have influenced the adaptation.
Reply to P Schrauwen et al

Dear Sir:

We are pleased that Schrauwen et al considered our article (1) significant enough to comment on the findings. Our study confirmed and, importantly, extended the work of Schrauwen et al (2) on the time course of adaptation to high-fat diets. The overall implication of our work is 2-fold. First, our results show that individuals are highly variable in their ability to switch off carbohydrate oxidation and increase fat oxidation when exposed to a high-fat diet. This observation was noted clearly at the end of the Results section of the article. The subjects in the study by Smith et al (3) showed energy balances ranging from –3084 to 1958 kJ (–737 to 468 kcal/d) (5). This range of energy balance was clearly greater than what we observed.

Similarly, Schrauwen et al argued that physically fit volunteers [ie, those with a high maximal oxygen uptake (VO2 max)] would have higher levels of spontaneous physical activity and therefore more negative energy balances. Again, their assumptions are incorrect. Energy balance was positively related to VO2 max (r² = 0.17; NS) in the opposite direction to that predicted by Schrauwen et al. This was likely due to our design, which adjusted scheduled physical activity and energy intake on the basis of the previous day’s energy balance (detailed in the Methods section).

Regarding the degree to which we were able to maintain energy balance, there are 2 important points to consider. First, in contrast with the protocols of Schrauwen et al, we directly measured both energy intake (duplicate meals) and fecal energy balance in our study. When we used nutrient database values during the conduct of the trial. When we used nutrient intake, there are 2 important points to consider. First, in contrast with the protocols of Schrauwen et al, we directly measured both energy intake (duplicate meals) and fecal energy balance during adaptation to a high-fat diet. Am J Clin Nutr 2000;71:450–7.

Last, Schrauwen et al failed to place our results in the context of other existing literature. In rats fed a high-fat diet, skeletal muscle oxidative capacity (6) and insulin sensitivity (7) were predictors of weight gain during high-fat feeding. These results are strikingly similar to our own.

In summary, the concerns of Schrauwen et al are not borne out by our data. Our ability to approach energy balance by using robust measures of energy intake, nonmetabolizable energy output, and indirect calorimetry was one of the major strengths of our investigation. We are confident in our results, which suggest that physical fitness and insulin sensitivity are important predictors of fat balance during acute high-fat feeding.

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REFERENCES


Effects of polyunsaturated fatty acids on psychiatric disorders

Dear Sir:

We are pleased to see the increased recognition of polyunsaturated fatty acids (PUFAs) in health promotion and medical treatment. However, a recent article in the Journal (1) covered many aspects of PUFAs but excluded many recent findings on psychiatric disorders, possibly because of the lag between the symposium and publication of the article. Empirical studies related to psychiatric disorders have focused on 1) assessment of PUFAs in the tissues (red blood cell membrane, platelet, fibroblast, and postmortem brain) of psychiatric patients, 2) therapeutic trials of PUFAs for the treatment of psychiatric disorders, and 3) evidence from the data of epidemiologic surveys.

Studies in primates suggested that the PUFAs concentrations of the red blood cell membrane can reflect the PUFA composition of frontal cortex (2). PUFAs are found to be depleted in the red blood cell membrane of patients with schizophrenia (3) and major depressive disorder (4). Horrobin et al (5) found decreased PUFAs in the frontal but not in the cerebellar cortex of postmortem brain tissue from schizophrenic patients. Tissue PUFAs deficiency has provided the rationale for treating symptoms of psychiatric disorders with n-3 fatty acids. The results of one open trial suggested that eicosapentaenoic acid might improve residual symptoms in schizophrenic patients (6). Furthermore, n-3 fatty acids exhibited mood-stabilizing properties in bipolar disorder in a recent pilot study (7). Thus, n-3 fatty acids may play an important role in the psychoneuroendocrinology of various psychiatric disorders.

From the epidemiologic data, societies consuming large amounts of fish, which contains more n-3 fatty acids than do other foods, appear to have a lower rate of major depression (8). Pekkanen et al (9) found that lower serum cholesterol was associated with a lower mortality rate from accidents and violence in coastal Western Finland. However, no association was found in Eastern Finland, which is located inland. Thus, the consumption of fish may be protective against psychiatric illnesses. These findings imply that PUFA concentrations might explain the controversial results concerning cholesterol and psychiatric disorders (10).

More than 65% of the dry weight of the brain is composed of lipids that play important structural and functional roles. Abnormalities in the PUFA composition of the brain can alter membrane microstructure and consequently affect brain function. We are not sure whether abnormality of PUFAs is of primary etiologic significance, secondary to the development of psychiatric disorders, or the result of other factors, such as diet, smoking, or treatment of psychiatric illness. More systemic studies involving PUFA analysis and supplementation in patients with psychiatric illnesses, controlling for confounding factors, are needed to resolve these issues.

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