Pergamon

Physiology & Behavior, Vol. 58, No. 1, pp. 75–79, 1995

0031-9384/95 $9.50 + .00

0031-9384(95)00028-3

Effects of Different Types of Isocaloric Parenteral Nutrients on Food Intake and Metabolic Concomitants

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Received 20 May 1994

BODOKY, G., M. M. MEGUID, Z.-J. YANG AND A. LAVIANO. *Effects of different isocaloric parenteral nutrients on food intake and metabolic concomitants.* PHYSIOL BEHAV **58**(1) 75–79, 1995.—Whether spontaneous food intake (SFI) is controlled by infused nutrient type or its caloric content, irrespective of nutrient type, was investigated. Rats were infused for 4 days with isocaloric solutions of different nutrient type but sharing the same intermediary metabolic oxidative pathway, providing 25% of daily caloric needs. One parenteral solution was a glucose, fat and amino acid mix (TPN-25%); the other provided ketone bodies (TRI-3.5%). Effects of parenteral infusions on SFI and metabolic concomitants were compared and contrasted to that in a group of orally fed rats. Both infusions reduced SFI by 50%. Rats receiving TRI-3.5% had lower blood glucose and insulin concentrations, but increased hepatic glycogen content compared to TPN-25% or orally fed rats. No differences in hepatic triglycerides occurred between the three groups. However, serum free fatty acids were significantly lower in TRI-3.5% and in TPN-25% groups vs. fed rats. Data indicate food intake suppression is mediated by caloric content rather than nutrient type, suggesting that a mediator of SFI regulation could be at the citric acid cycle level.

Spontaneous food intake Total caloric intake Intravenous nutrient infusions Parenteral nutrients
Ketone bodies Glucose Insulin Free fatty acids Triglycerides Glycogen Citric acid cycle
Control food intake Rat

INTRODUCTION

NUMEROUS theories regarding the control of spontaneous food intake (SFI) have been proposed. Theories based on the three macronutrients (14,16,19) propose that daily food intake is modulated by nutrient-specific sensor cells, able to sense the presence of these nutrients and to signal this information to the food intake regulating areas in the brain (22,29). This implies that specific sensing cells exist for every conceivable nutrient; not only for glucose (21) and amino acids (26), but also for ethanol (12) and maybe for fat and other nutrients too. In such a model, food intake is regulated by the cumulative activity of each different sensor type (30). In an alternative model, food intake is regulated by a biochemical event common to all nutrients and occurring beyond a nutrient specific receptor(s) (10), irrespective of the nutrient type. The purpose of this study was to determine if SFI is mediated by either the nutrient type or by its caloric content irrespective of the nutrient type.

Since parenteral infusion of nutrients depress SFI in humans (11,25) and in animals (7,18,29), the anorectic effect of total parenteral nutrition (TPN) has been used as a model to obtain some insights relative to the control of normal food intake, because it bypasses pre and early postingestive stimuli. Thus, using a rat model, we compared the effects on SFI, total caloric intake (TCI) and metabolic concomitants of two isocaloric parenteral solutions, differing in the type of nutrient infused, but sharing the same final common oxidative pathway. One solution type was a well-balanced TPN mixture, containing glucose, fat and amino acids, while the other consisted of triacetin, providing ketone bodies as energy substrate. The results were contrasted with the same parameters obtained in a group of orally fed rats, serving as controls.

MATERIALS AND METHODS

Male Fischer 344 rats (Charles River Inc., Wilmington, MA), with a purchase weight of 260–290 g, were individually housed in holding cages to acclimatize them to the constant study surroundings [12 h light/dark cycle (0600 h–1800 h), room temperature of 26 ± 1°C]. Rats had free access to water and coarsely ground rat chow (Diet #5008, Ralston Purina, St. Louis, MO), which provided 3.5 Kcal/g. The caloric ratio of carbohydrate to fat and to amino acids was 50:30:20. Daily SFI was measured gravimetrically at 0800 h. After 10 days of acclimatization, rats which gained weight and appeared healthy, were entered into a study which had been approved by the Committee for the Hu-

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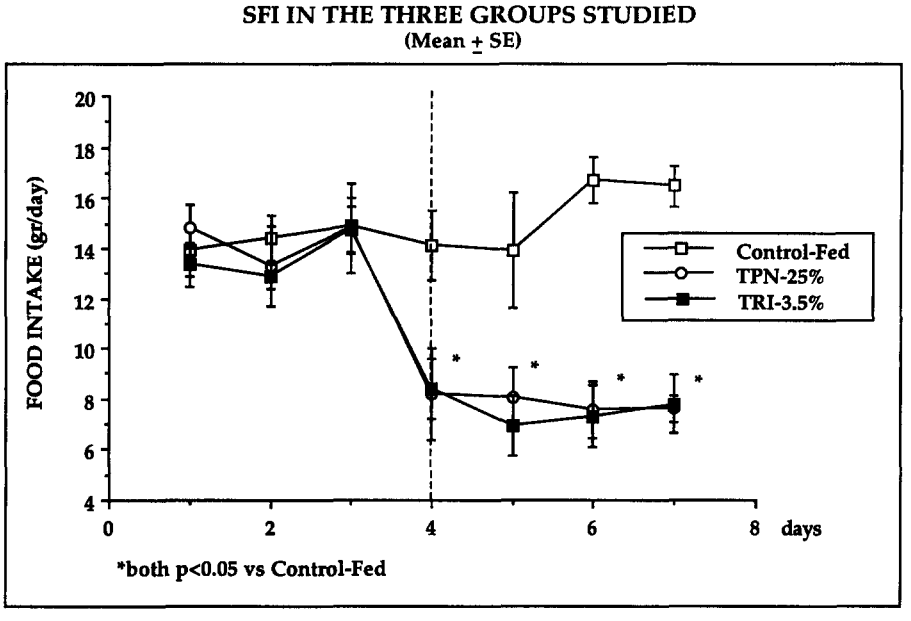

FIG. 1. Spontaneous food intake in the 3 groups of rats. Between days 4 and 7, the TPN-25% and TRI-3.5% groups received 25% of their calorie requirement by parenteral administration, the TPN-25% group from a mixed nutrient solution and the TRI-3.5% group from a 3.5% triacetin solution.

mane Use of Animals at SUNY Health Science Center at Syracuse.

Study Design and Procedures

An internal jugular catheter (Silastic Medical Grade Tubing, Dow Corning Co., Midland, MO) was placed aseptically under anesthesia, as previously described (18). Briefly, after catheterization of the internal jugular vein, the catheter was exteriorized at the nape of the neck via a SC tunnel, and protected by a weighted spring and swivel device sutured to the skin of the neck. Catheter patency was maintained with a constant infusion of normal saline at 3 ml/h. Thereafter, the rats were placed in individual metabolic cages to measure food intake. Total caloric intake was also calculated. Chow and water were available throughout the study. Rats were weighed just prior the insertion of the internal jugular catheter and at the end of the experiment. Ten days after surgery, the rats were randomized into three treatment groups:

TPN-25% group. Eight rats were infused for 3 days with normal saline at 3 ml/h, and then with a mixed fuel parenteral nutrient solution (glucose, fat, amino acids) for 4 days (3 ml/h), providing 25% of the rat's daily caloric needs. The caloric ratio of glucose to fat (Intralipid 20%; Kabi Vitrum, Stockholm, Sweden) and to a well-balanced amino acid solution (Novamine; Kabi Vitrum) was 50:30:20 (18).

TRI-3.5% group. The second set of 8 rats were infused for 3 days with normal saline at 3 ml/h, and then with a 3.5% triacetin solution at 3 ml/h for 4 days (Triacetin; Sigma Chemical Co., St. Louis, MO), providing 25% of the rat's daily caloric needs.

All rats had free access to chow and water during the study and were decapitated, on day 7, after 4 days of parenteral infusion for biochemical sampling of blood and liver.

Control-Fed group. Eight rats had free access to water and fresh coarsely ground chow for 7 days. Rats were sacrificed for blood and tissue samples, immediately after decapitation, at the same time as the two parenteral infusion groups.

Sampling and Preparations of Materials

Rats were decapitated and mixed arterio-venous trunk blood was collected in EDTA tube, which was immediately centrifuged at +4°C. Plasma was separated and frozen at −30°C until assayed. Using a freeze clamp technique, whole liver was rapidly harvested with tongs precooled in liquid nitrogen and were stored at −70°C.

Chemical Determinations

Plasma glucose was measured by the hexokinase method (Sigma Diagnostic, St. Louis, MO). Serum free fatty acids (FFA) were measured using an enzymatic calorimetric method for quantitative determination (Wako Pure Chemical Industries, Osaka, Japan). Plasma insulin was measured by RIA using a 125-J Insulin RIA kit (Cambridge Medical Diagnostic, Billerica, MA). Liver glycogen and triglyceride measurements were made based on the methods of Hassid and Abraham (13), and Denton and Randle (6), respectively.

Statistical Analysis

ANOVA multi-comparison was used to compare the food and caloric intake data. Plasma glucose, serum FFA, plasma insulin and liver glycogen and triglyceride content were similarly compared in all groups. The data are expressed as mean ± standard error.

RESULTS

Body Weight, Food Intake and Total Caloric Intake

At the end of the study, the 24 rats constituting the TPN-25%, TRI-3.5% and Control-Fed groups had a mean body weight gain of 3.8%, 4.5%, and 4.5%, respectively. These data confirm that rats were healthy and were receiving adequate nutrient support.

The mean SFI for the three groups prior to the treatment was 14.0 ± 1.1 g/day. In the Control-Fed group, no change in SFI

occurred thereafter (Fig. 1). When TPN-25% and TRI-3.5% were infused, SFI decreased in each group significantly ($p < 0.05$). By the fourth day of infusion, TPN-25% and TRI-3.5%, which provided only 25% of total daily caloric intake, decreased SFI by approximately 50% and was 7.6 ± 0.5 g/day and 7.8 ± 1.1 g/day ($p < 0.05$), respectively (Fig. 1). The two types of isocaloric solutions depressed SFI by the same amount, there being no difference in the degree of SFI depression between them.

In the three days prior to the treatment, the mean daily caloric intake for the three groups was 49 ± 3.8 Kcal (Table 1). Total caloric intake was significantly depressed and to the same degree by both TPN-25% and TRI-3.5%. On day 7, it was 39.7 ± 1.7 Kcal/day and 40.4 ± 3.8 Kcal/day, respectively (Table 1). No change in TCI occurred in Control-Fed group (Table 1).

Plasma

Glucose. As shown in Fig. 2, after 4 days of treatment, the concentration of plasma glucose was 151 ± 3 mg/dl in TPN-25% group, 137+2 mg/dl in TRI-3.5% group and 154 ± 2 mg/dl in Control-Fed group. There was no difference between the plasma glucose concentrations of Control-Fed and TPN-25% group, both of which were significantly higher ($p < 0.05$) than that of the TRI-3.5% group.

Free fatty acids. Serum FFA concentration was 0.54 ± 0.06 mEq/L in TPN-25% group, 0.59 ± 0.03 mEq/L in TRI-3.5% group and 0.69 ± 0.03 mEq/L in Control-Fed groups. As shown in Fig. 2, the Control-Fed group had significantly higher ($p < 0.05$) FFA concentration than the TPN-25% or TRI-3.5% groups. There was no difference in the serum FFA concentration between the TPN-25% and TRI-3.5% groups (Fig. 2).

Insulin. As shown in Fig. 2, the plasma insulin concentration was 53 ± 4 μU/ml in TPN-25% group, 35 ± 2 μU/ml in TRI-3.5% group and 60 ± 4 μU/ml in Control-Fed group. There was no difference in insulin concentration between the Control-Fed and TPN-25% groups. But plasma insulin concentration in the TRI-3.5% group was significantly lower than in the TPN-25% group ($p < 0.05$).

Liver

Glycogen. As shown in Fig. 3, the liver glycogen concentration was 42.1 ± 4.9 mg/g wet tissue in TPN-25% group, 65.9 ± 3.9 mg/g wet tissue in TRI-3.5% group and 50.4 ± 1.6 mg/g wet tissue in Control-Fed group. As expected, there was no difference in liver glycogen concentration between Control-Fed and TPN-25% groups. But liver glycogen content was significantly ($p < 0.05$) higher in the TRI-3.5% group than in either TPN-25% or Control-Fed groups.

TABLE 1

FOOD AND CALORIC INTAKE IN THE THREE GROUPS STUDIED

Intake	Day 3	Day 7	*p*
Food (g/day)			
Control-Fed	14.8 ± 1.4	16.3 ± 0.3	NS
TPN-25%	14.6 ± 0.5	7.6 ± 0.5	0.05
TRI-3.5%	14.5 ± 0.5	7.8 ± 1.1	0.05
Caloric (kcal/day)			
Control-Fed	51.8 ± 4.9	57.0 ± 1.0	NS
TPN-25%	51.5 ± 1.7	39.7 ± 1.7	0.05
TRI-3.5%	50.7 ± 1.8	40.4 ± 3.8	0.05

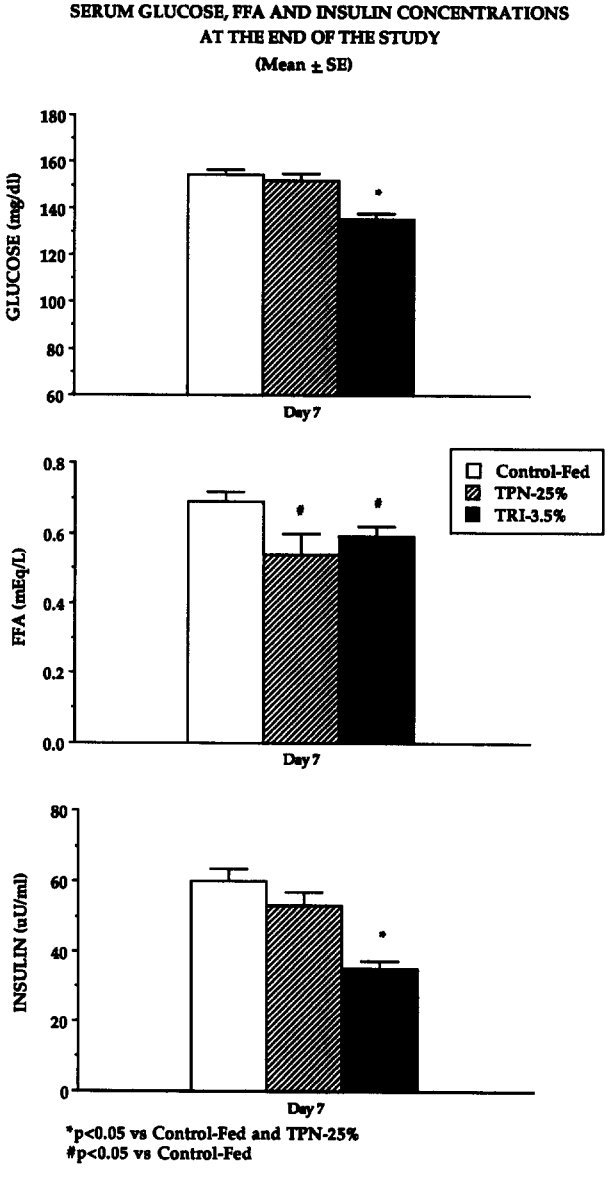

FIG. 2. Plasma glucose, free fatty acid (FFA) and insulin concentrations on day 7.

Triglycerides. The liver triglyceride concentration was 10.6 ± 1.2 mg/g wet tissue in TPN-25% group, 9.8 ± 1.8 mg/g wet tissue in TRI-3.5% group and 11.3 ± 0.5 mg/g wet tissue in Control-Fed group, there being no difference in liver triglyceride concentration among the groups (Fig. 3).

DISCUSSION

Our data confirm that: (i) parenteral nutrients depress SFI; (ii) isocaloric nutrients of different types suppress SFI by comparable amounts; and (iii) providing 25% of daily calories parenterally led to approximately a 50% decrease in SFI. According to the data, hepatic glycogen does not seem to play a role in the regulation of SFI because glycogen content was significantly different in the TRI-3.5% and TPN-25% groups, despite a similar depression of SFI. These data are in agreement with previous studies showing that the two measures (caloric intake and glycogen synthesis rate) are not related (17,27,28). Hepatic triglyceride con-

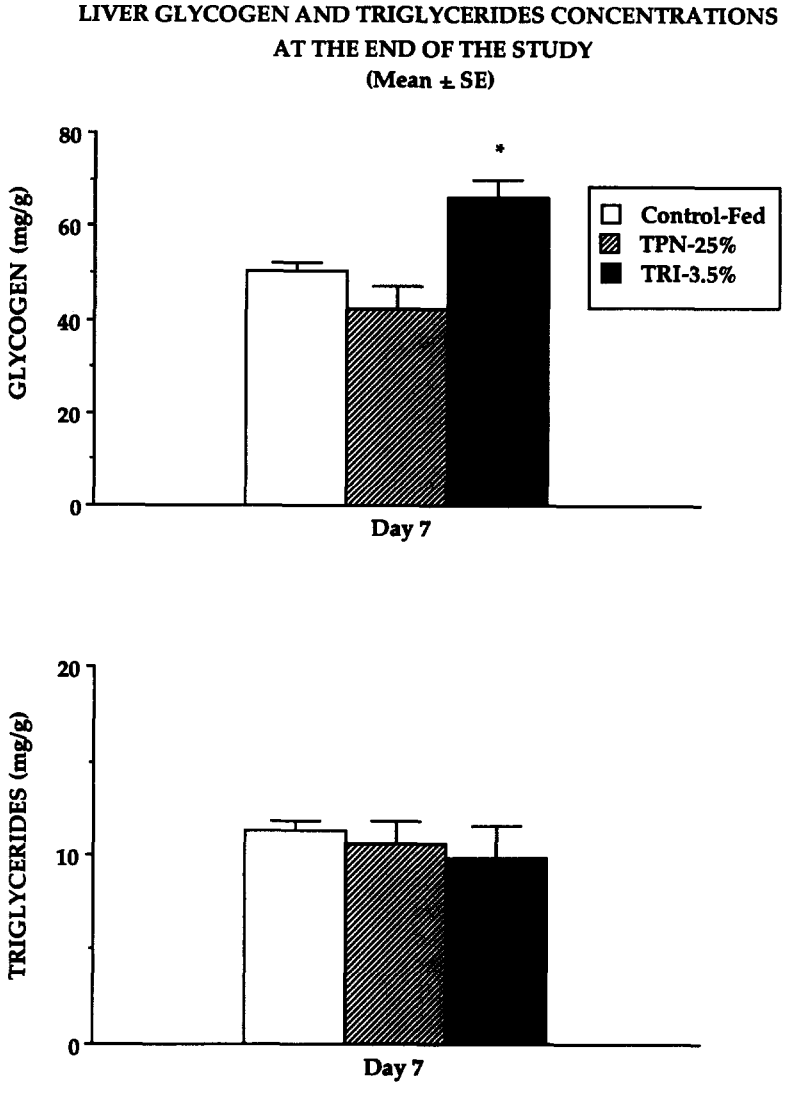

FIG. 3. Liver glycogen and triglyceride concentrations on day 7.

tents were comparable in the three groups studied even though SFI and TCI were markedly different, again suggesting that their role in the reduction of SFI in this study design is minimal. Similarly, plasma insulin and blood glucose concentrations were significantly different between TPN-25% and TRI-3.5% groups, yet animals in both groups ate the same amount of food and thus received the same quantities of calories.

Serum FFA concentrations showed an interesting trend. In both TRI-3.5% and TPN-25% groups, FFA concentrations were significantly lower than in the Control-Fed group, suggesting that fat oxidation could be involved in the integrated control of food intake, as supported by our previous studies (3,4), pointing to an inverse relationship between fat fuel oxidation and food intake. Food intake decreases when rates of fatty acid oxidation are high, whereas, under conditions in which fat oxidation is low and fat storage is favored, food intake tends to increase (7). Although food intake is likely to be modulated by signals associated with body fat content, recent work postulated that feeding is controlled by an event common to the metabolism of carbohydrate and fat, and thus occurs after glycolysis and beta-oxidation (3,9,24).

The mechanisms by which liver recognizes the amount of calories infused or ingested are still incompletely understood. Specific cell types in the liver that sense the presence of glucose and amino acids and which then connect with hypothalamus via the vagus have been identified in the hepato-portal system in animals (21,22,26). Because a variety of other sensors have also been identified (23) which are also connected with the hypothalamus via vagal innervation (1), it is therefore conceivable that there are as many different nutrient sensor types as there are possible nutrient sources (29). An alternative hypothesis has been proposed by Friedman et al. (8), postulating that SFI could be regulated via an integrated control, in which the amount of energy infused or ingested, irrespective of nutrient type, is the common denominator.

In line with this reasoning, the effects on SFI of two isocaloric parenteral solutions, differing in nutrient composition, metabolic pathways and metabolic consequences, but sharing the same final oxidative step via the citric acid cycle, was compared. To test this hypothesis, we used a standard TPN mixture, which provides glucose, lipids, and amino acids, while the other solution pro-

vided triacetin, the water soluble triglyceride of acetate, as unique energy substrate. Triacetin is readily hydrolyzed in the bloodstream into glycerol and acetate (2); transformed respectively in glucose and acetyl-CoA by the liver and oxidized in the citric acid cycle (5,15).

Our observation that both isocaloric infusions decrease SFI to the same extent, regardless of their different nutrient compositions and/or their metabolic consequences, is consistent with the hypothesis that SFI is regulated by the activity of a specific energy sensor, which senses the amount of calories infused.

This hypothesis is also supported by evidence that the infusion of graded caloric loads using well balanced TPN formulas results in a parallel and almost complete reduction of food intake (18). No change in SFI (31) or a lower caloric compensation (20,29,30) have been reported in the literature when a variety of single nutrients alone were infused. Although these data may be interpreted as a failure of the energy sensor to recognize total energy infused, it is more likely that they reflect an attempt to maintain the normal composition of incoming essential nutrients, as suggested by the observations of Nicolaidis and Rowland that "the less nutritionally balanced the infusion, the less the reduction in food intake" (20).

In summary, our data indicate that energy sensor could be related to the citric acid cycle because the two different parenteral formulas administered in this study shared the same final oxidative pathway. It has been suggested that mitochondrial transport of fatty acids may play a role in the regulation of SFI (9). An alternative hypothesis is that the energy provided by any nutrient infused or ingested is utilized for some biochemical event. The end product of this metabolic pathway could then act as a second messenger capable to inform, via the vagus nerve, the brain on the nutritional status of the organism.

ACKNOWLEDGEMENTS

We thank Ms. Darlene Thompson for her diligent editorial assistance. Work presented in this paper is supported in part by Grant 930258 from the Hendricks Fund for Medical Research, Syracuse, NY; and Grant DK43796 from the National Institute of Diabetes, Digestive and Kidney Diseases.

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