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Glutamine force-feeding effect on plasma amino-acid concentrations in growing rats fed a cafeteria diet

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Summary — The effect of a glutamine force-feeding on plasma amino-acid levels in rats fed either a reference diet or a cafeteria diet was studied during weaning. The increases in plasma amino-acid levels shown by rats eating the cafeteria diet were related to the force-feeding and/or the age studied. The glutamine solution decreased the levels of proline, ornithine and tyrosine in the plasma of rats eating the cafeteria diet. In rats fed the reference diet, glutamine solution increased the plasma concentrations of threonine and cysteine. A major effect of diet over force-feeding was shown.

glutamine / force-feeding / cafeteria diet / growing rat / amino acid

Résumé — Effets d'un gavage de glutamine sur les concentrations plasmatiques en amino-acides chez des rats en croissance alimentés en cafeteria. L'effet de l'administration orale d'une solution de glutamine sur les concentrations des acides aminés plasmatiques chez le rat nourri avec une alimentation de référence ou une alimentation de type cafeteria a été étudié pendant leur développement. Les variations des acides aminés chez le rat nourri avec une alimentation en cafeteria dépendent du gavage et/ou de l'âge étudiés. Nous avons observé une diminution des concentrations de proline, ornithine et tyrosine dans le plasma des rats nourris avec l'alimentation en cafeteria en utilisant un gavage avec la glutamine. En revanche, chez les rats nourris avec l'aliment de référence, le gavage avec la glutamine a provoqué une augmentation des concentrations plasmatiques de thréonine et de cystéine. L'effet de l'alimentation en cafeteria est plus important que celui du gavage avec la glutamine.

glutamine / gavage / alimentation en cafeteria / rat en croissance / acides aminés

INTRODUCTION

The cafeteria diets were introduced as a way to generate an animal model of obesity that is closer than genetic obesity to the situation in humans consuming highly palatable choice diets (Sclafani and Springer, 1976). Cafeteria diets may differ somewhat in composition, but it has been shown that despite of a highly variable selection of food, the nutrient composition of the diet ingested is fairly constant (Prats *et al*, 1989). The diets actually selected by the rats have a common high lipid content (Naim *et al*, 1985), with relatively unchanged, and proportionally lower, protein and carbohydrate contents (Prats *et al*, 1989). Constant exposure to these diets from birth results in high growth rates (Salvadó *et al*, 1986), with high increases in energy intake (Prats *et al*, 1989) and increased thermogenesis (Rothwell and Stock, 1982). A cafeteria diet increased the retention of dietary nitrogen (Barr and McCracken, 1984) and lowered urinary nitrogen losses (Barber *et al*, 1985); nitrogen accretion in the body was the highest for the younger animals (Esteve *et al*, 1992). The amino-acid composition of the diet ingested by reference and cafeteria diet-fed rats has been analyzed: a cafeteria diet results in a higher proportion of amino acids extracted from the diet, although this diet had a very similar amino-acid composition to that of the standard reference diet (Esteve *et al*, 1993; Rafecas *et al*, 1993). The individual amino acids best absorbed by young Wistar rats fed a cafeteria diet were Ala, Ser, Hyp, Tyr, Thr and Lys (Esteve *et al*, 1993).

Glutamine is now classified as a conditionally essential amino acid (Smith, 1990) indicating that a dietary source is required under metabolic stress (Meijer *et al*, 1993) or certain pathologic conditions (Mobrahan, 1992), especially those concerning the intestinal tract (Souba, 1993). However, in normal physiological conditions glutamine

is not an essential amino acid, and we have supplied it here as a source of non-essential nitrogen. The supplementation of a cafeteria diet with an essential amino-acid mixture showed a synergism between the 2 treatments on nitrogen retention (Salvadó and Arola, 1992a), growth (Salvadó and Arola, 1992a) and amino-acid availability (Salvadó and Arola, 1993) in weaning rats. The present study was designed to investigate the effects of administering oral glutamine solution on the plasma concentrations of amino acids in cafeteria-diet-fed or reference-diet-fed young rats in comparison with a previous force-feeding with essential amino acids (Salvadó and Arola, 1992a; Salvadó and Arola, 1993).

MATERIALS AND METHODS

Sixty weaning rats (14, 20 and 30 d of age) were used. Litters were randomized to 8 pups at delivery and kept with their mothers until sacrifice. Primiparous Wistar rats were kept individually in polypropylene-bottomed cages with wood shavings as absorbent material. The cages were housed in a room with controlled temperature (21–22°C), humidity (75–85%) and lighting (lights on from 8 to 20 h). From mothers fed one of the 2 diets *ad libitum* (reference diet or cafeteria diet) pups were divided randomly into 4 groups ($n = 5$) on d 11 after birth: saline-reference; saline-cafeteria; glutamine-reference; glutamine-cafeteria. The pups were given a daily solution at a dose of 10 ml/kg body weight by means of a stomach canula between 9 and 10 am on postnatal d 11. The composition of the force-fed solutions was: a) 9 g/l sodium chloride (saline) in Tween 90 solution; or b) 30 g/l glutamine in Tween 90. The composition of the 2 diets were: a) reference diet: standard pellet (A04 from Panlab, Barcelona) and tap water; and b) cafeteria diet: fresh pastry, cookies, chocolate, bacon, Swiss cheese, candy, roasted hazelnuts, banana, liver pate, chow pellets (as indicate above), tap water and whole milk complemented with 250 g/l sucrose and 15 g/l of a protein and mineral supplement (Gevral Proteina, Cyanamid Iberica, Barcelona). All the materials were presented daily in excess. The total energy intake of reference diet was 1438.5 kJ/d.kg rat

(1036 kJ/d.kg from carbohydrate; 98.5 kJ/d.kg from fat; and 304.5 kJ/d.kg from protein). The total energy intake of the self-selected cafeteria diet was 2463 kJ/d.kg rat (1191 kJ/d.kg from carbohydrate; 932.5 kJ/d.kg from fat; and 339.5 kJ/d.kg from protein). A more detailed description of the diet was given previously (Prats *et al*, 1989).

Pups were killed by decapitation on postnatal d 14, 20 or 30. Blood samples were collected in dry heparinized beakers. Plasma was obtained by centrifugation, and small aliquots were deproteinized with cold acetone. The individual amino acids were determined in clear supernatants, after their derivatization with dansyl chloride labelled with ^{14}C , chromatographic separation and evaluation of the radioactivity present (Arola *et al*, 1976; Arola *et al*, 1977). Glutamate plus glutamine, aspartate plus asparagine and leucine plus isoleucine, are given as composite values, due to methodological considerations. Statistical comparisons between groups were performed with 3-factor ANOVA test (Dixon *et al*, 1983). The 3-way ANOVA implies the factors: diet, age and force-feeding. When there were no significant interactions between the 3 factors, the results obtained from this analysis were considered; otherwise, 2-way ANOVAs were carried out. All data are expressed as mean \pm SEM. In all analyses, differences were considered significant at $P < 0.05$.

RESULTS

The final body weight was significantly lower in glutamine than saline force-fed rats; it was also lower in the reference-diet-fed than in cafeteria-diet-fed rats. On d 30, body weights were 76.50 g for saline-reference, 56.60 g for glutamine-reference, 82.67 g for saline-cafeteria and 65.38 g for glutamine-cafeteria.

Table I shows the amino-acid concentrations in the plasma of the 4 groups, measured on d 14, 20 and 30. An overall increase in plasma amino-acid levels is shown by rats fed the cafeteria diet as was previously seen (Calles-Escandon *et al*, 1984; Rafecas *et al*, 1991; Salvadó *et al*, 1991; Salvadó and Arola, 1993). This

increase is especially evident in glucogenic amino acids and in imino acids and is also shown in some basic amino acids: arginine and citrulline, in the branched-chain amino acid valine and in the sulphur amino acid cysteine. However, these increases, with the only exception of glutamine + glutamate concentrations, are affected by the force-feeding and/or the age studied.

Glutamine force-feeding decreased the levels of proline, ornithine and tyrosine in the plasma of rats eating the cafeteria diet; alanine, serine, hydroxyproline, arginine, histidine and leucine + isoleucine were also lower in these rats, but only at 14 d or, in the case of valine, at 20 d. Conversely, glutamine force-feeding increased the plasma levels of threonine at 20 and 30 d, those of citrulline at 20 d and those of leucine + isoleucine and tryptophan at 30 d, when rats were fed the cafeteria diet. On the other hand, in rats fed the reference diet, glutamine force-feeding increased the plasma concentrations of threonine and cysteine, and also those of histidine only at 20 d. Glutamine force-feeding also increased the plasma levels of aspartate + asparagine at 20 d, but after a decrease at 14 d. Methionine and phenylalanine showed no significant difference for the analyzed factors.

Plasma concentrations of alanine, leucine + isoleucine and tryptophan of cafeteria-diet-fed rats changed with age when they were force-fed with glutamine but not when the force-feeding was with the saline solution. Conversely, the variations with age of hydroxyproline and arginine levels seen in the plasma of saline force-fed rats, disappeared when glutamine solution was administered. The developmental patterns showed by serine, threonine, histidine, citrulline and valine also depended on the force-feeding supplied in rats eating the cafeteria diet. However, the changes shown with age by glycine, proline, ornithine, cysteine, taurine and tyrosine were independent of force-feeding in the 2 diets supplied, as

Table I. Amino-acid concentrations in the plasma of 14, 20 and 30 d glutamine or saline force-fed rats eating a reference or cafeteria diet.

	Age (d)	Saline reference	Saline cafeteria	Glutamine reference	Glutamine cafeteria	ANOVA
<i>Gluconeogenic amino acids</i>						
alanine	14	0.83 ± 0.11	1.47 ± 0.14	0.83 ± 0.05	0.81 ± 0.04↓	D,A,I
	20	0.80 ± 0.11	1.46 ± 0.12	1.22 ± 0.11	1.69 ± 0.13	
	30	1.02 ± 0.10	1.57 ± 0.14	1.01 ± 0.09	1.79 ± 0.14	
glutamate + glutamine	14	0.89 ± 0.07	1.30 ± 0.15	0.81 ± 0.03	0.87 ± 0.05	D,A
	20	0.83 ± 0.03	1.23 ± 0.06	0.89 ± 0.04	1.11 ± 0.13	
	30	1.20 ± 0.12	1.70 ± 0.16	1.17 ± 0.23	1.54 ± 0.12	
aspartate + asparagine	14	0.04 ± 0.007	0.06 ± 0.006	0.03 ± 0.000	0.04 ± 0.006	D,I
	20	0.02 ± 0.004	0.04 ± 0.005	0.05 ± 0.005	0.05 ± 0.006	
	30	0.03 ± 0.002	0.04 ± 0.007	0.03 ± 0.007	0.04 ± 0.006	
glycine	14	0.51 ± 0.04	0.75 ± 0.07	0.36 ± 0.02	0.43 ± 0.02	D,I
	20	0.69 ± 0.04	1.11 ± 0.04	0.99 ± 0.08	1.16 ± 0.12	
	30	0.87 ± 0.15	1.76 ± 0.25	1.00 ± 0.11	1.42 ± 0.19	
serine	14	0.33 ± 0.04	0.61 ± 0.07	0.31 ± 0.03	0.34 ± 0.08↓	D,A,I
	20	0.52 ± 0.06	0.87 ± 0.08	0.77 ± 0.04	0.75 ± 0.07	
	30	0.41 ± 0.04	0.69 ± 0.09	0.42 ± 0.02	0.76 ± 0.09	
threonine	14	0.15 ± 0.01	0.25 ± 0.02	0.16 ± 0.02↑	0.22 ± 0.01	D,G,A,I
	20	0.24 ± 0.03	0.27 ± 0.02	0.38 ± 0.02↑	0.41 ± 0.07↑	
	30	0.24 ± 0.02	0.29 ± 0.04	0.29 ± 0.02↑	0.42 ± 0.03↑	
<i>Imino acids</i>						
proline	14	0.43 ± 0.02	0.66 ± 0.03	0.41 ± 0.02	0.40 ± 0.04↓	D,A,I
	20	0.54 ± 0.02	0.74 ± 0.09	0.70 ± 0.05	0.68 ± 0.05↓	
	30	0.46 ± 0.06	0.95 ± 0.01	0.44 ± 0.06	0.77 ± 0.08↓	
hydroxyproline	14	0.14 ± 0.01	0.23 ± 0.02	0.13 ± 0.01	0.11 ± 0.01↓	D,A,I
	20	0.07 ± 0.01	0.11 ± 0.01	0.13 ± 0.02	0.10 ± 0.01	
	30	0.06 ± 0.00	0.12 ± 0.02	0.08 ± 0.02	0.11 ± 0.03	
<i>Basic amino acids</i>						
lysine	14	0.48 ± 0.01	0.59 ± 0.02	0.58 ± 0.13	0.56 ± 0.08	A
	20	0.46 ± 0.04	0.33 ± 0.04	0.47 ± 0.06	0.34 ± 0.05	
	30	0.47 ± 0.03	0.40 ± 0.03	0.49 ± 0.04	0.38 ± 0.08	
arginine	14	0.26 ± 0.02	0.68 ± 0.15	0.24 ± 0.01	0.32 ± 0.03↓	D,A,I
	20	0.44 ± 0.07	0.64 ± 0.06	0.66 ± 0.08	0.54 ± 0.03	
	30	0.27 ± 0.03	0.32 ± 0.07	0.26 ± 0.06	0.36 ± 0.08	
histidine	14	0.21 ± 0.03	0.28 ± 0.03	0.16 ± 0.01	0.28 ± 0.02↓	A,I
	20	0.11 ± 0.01	0.09 ± 0.01	0.17 ± 0.02↑	0.12 ± 0.01	
	30	0.07 ± 0.01	0.12 ± 0.01	0.08 ± 0.02	0.09 ± 0.01	

Table I. Cont

	Age (d)	Saline reference	Saline cafeteria	Glutamine reference	Glutamine cafeteria	ANOVA
citrulline	14	0.02 ± 0.002	0.05 ± 0.003	0.02 ± 0.002	0.02 ± 0.004	D,A,I
	20	0.09 ± 0.010	0.10 ± 0.003	0.10 ± 0.002	0.13 ± 0.013↑	
	30	0.06 ± 0.010	0.08 ± 0.005	0.07 ± 0.006	0.10 ± 0.015	
ornithine	14	0.20 ± 0.01	0.26 ± 0.02	0.14 ± 0.02	0.17 ± 0.02↓	G,A,I
	20	0.17 ± 0.01	0.16 ± 0.02	0.17 ± 0.01	0.16 ± 0.02↓	
	30	0.11 ± 0.02	0.13 ± 0.01	0.13 ± 0.01	0.07 ± 0.01↓	
<i>Branched-chain amino acids</i>						
valine	14	0.20 ± 0.03	0.31 ± 0.01	0.21 ± 0.02	0.24 ± 0.01	D,A,I
	20	0.40 ± 0.04	0.54 ± 0.08	0.45 ± 0.05	0.37 ± 0.05↓	
	30	0.32 ± 0.01	0.34 ± 0.01	0.30 ± 0.03	0.43 ± 0.05	
leucine + isoleucine	14	0.27 ± 0.04	0.29 ± 0.04	0.22 ± 0.02	0.19 ± 0.01↓	I
	20	0.19 ± 0.02	0.22 ± 0.01	0.23 ± 0.01	0.15 ± 0.01	
	30	0.17 ± 0.02	0.18 ± 0.02	0.17 ± 0.03	0.28 ± 0.05↑	
<i>Sulphur-containing amino acids</i>						
cysteine	14	0.007 ± 0.001	0.010 ± 0.001	0.009 ± 0.001↑	0.011 ± 0.002	D,A,I
	20	0.009 ± 0.001	0.020 ± 0.004	0.017 ± 0.004↑	0.015 ± 0.002	
	30	0.003 ± 0.005	0.008 ± 0.001	0.008 ± 0.001↑	0.007 ± 0.001	
methionine	14	0.04 ± 0.005	0.06 ± 0.005	0.05 ± 0.009	0.03 ± 0.007	
	20	0.05 ± 0.007	0.05 ± 0.010	0.06 ± 0.010	0.06 ± 0.012	
	30	0.03 ± 0.005	0.04 ± 0.010	0.03 ± 0.004	0.06 ± 0.017	
taurine	14	0.13 ± 0.01	0.26 ± 0.03	0.14 ± 0.01	0.17 ± 0.02	A,I
	20	0.77 ± 0.04	0.77 ± 0.04	0.95 ± 0.08	0.64 ± 0.11	
	30	0.24 ± 0.03	0.35 ± 0.06	0.34 ± 0.05	0.48 ± 0.09	
<i>Aromatic amino acids</i>						
tyrosine	14	0.12 ± 0.01	0.15 ± 0.01	0.13 ± 0.01	0.13 ± 0.01↓	A,I
	20	0.36 ± 0.03	0.61 ± 0.07	0.54 ± 0.04	0.43 ± 0.03↓	
	30	0.06 ± 0.01	0.12 ± 0.01	0.10 ± 0.01	0.10 ± 0.01↓	
tryptophan	14	0.12 ± 0.01	0.15 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	A,I
	20	0.15 ± 0.02	0.19 ± 0.01	0.21 ± 0.02	0.16 ± 0.01	
	30	0.18 ± 0.02	0.20 ± 0.01	0.22 ± 0.04	0.30 ± 0.02↑	
phenylalanine	14	0.08 ± 0.01	0.08 ± 0.01	0.10 ± 0.02	0.12 ± 0.02	
	20	0.06 ± 0.01	0.17 ± 0.01	0.20 ± 0.05	0.12 ± 0.05	
	30	0.08 ± 0.01	0.10 ± 0.02	0.13 ± 0.03	0.15 ± 0.05	

Amino-acid concentrations are expressed in mM. Statistical significance (ANOVA) of the comparisons: for diet: D; for age: A; for force-feeding: G; for interaction among the comparisons done: I. The symbols ↓ and ↑ represent that the values were lower or higher, respectively, in glutamine than in saline force-fed pups.

were the serine, threonine, hydroxyproline, arginine, citrulline, valine, leucine + isoleucine and tryptophan concentrations in the plasma of animals fed the reference diet. Asparagine + aspartate and histidine changed with age depending on force-feeding in rats fed the reference diet. Glutamine + glutamate and lysine showed a developmental patterns similar for the several diets and solutions supplied.

DISCUSSION

In a previous report (Salvadó and Arola, 1992b) it could be demonstrated that glutamine force-feeding enhanced urea production and liver adenylate deaminase activity and inhibited liver glutamine synthetase and serine dehydratase activities in chow-fed pups. Minor effects of glutamine force-feeding were shown in the already modified activities of nitrogen metabolism enzymes in the livers of cafeteria-fed rats (Salvadó and Arola, 1992b).

The amino-acid percentage composition of the diet selected by cafeteria rats was practically identical to that of the reference diet (Rafecas *et al*, 1993). However, cafeteria-diet-fed rats had a higher dietary protein digestion/absorption efficiency than reference-diet-fed animals (Rafecas *et al*, 1993). This is probably due to changes induced by diet in the intestinal amino-acid transport systems, and is in agreement with the modulation of intestinal amino-acid transport by energy availability (Karasov *et al*, 1987) and physiological conditions (Israel *et al*, 1968; Schedl, 1974). Further, the lower proportion of protein (not amount) in the cafeteria diet could explain the higher intestinal absorption of protein amino acids (Esteve *et al*, 1993).

In general, the changes in plasma amino-acid concentrations caused by glutamine force-feeding are different when rats are eating cafeteria diet or reference diet. In rats

eating the cafeteria diet, the decreases are shown in some plasma amino acids, and in rats eating the reference diet increases are shown in other amino acids. This could be explained because nutrient delivery has been shown to influence glutamine transport activity in the gut mucosa (Souba, 1993). On the other hand, the increased quantities of circulating ketone bodies in cafeteria-fed pups (Salvadó and Arola, 1992b) may have a suppressive effect on the oxidation of glutamine in the intestine (Nagy and Kretchmer, 1988).

A dose-related increase in human serum concentrations was reported for glutamine as well as for alanine, citrulline, and arginine (which are considered as the end products of glutamine metabolism) after oral glutamine administration (Ziegler *et al*, 1990). The results obtained in the present study disagree with this, the only agreement being the higher levels of citrulline at 20 d in cafeteria-diet-fed rats. Conversely, proline – another end product of intestinal glutamine metabolism – is decreased by glutamine force-feeding in cafeteria-diet-fed pups. Further, alanine and arginine are lower at d 14 in the same rats. The decreased concentrations shown by some amino acids only at 14 d could be related to the fact that rat pups begin to nibble solid food at d 14 (Babicky *et al*, 1973). However a posterior adaptation to glutamine force-feeding is shown on the following studied days. It is also conceivable that the provision of glutamine to the intestine by the oral route may decrease the uptake of glutamine from the circulation (Moundras *et al*, 1993). A lowered sulphur intake has been described in rats fed the cafeteria diet (Fernandezlopez *et al*, 1993). However, we have found higher plasma cysteine levels in cafeteria-fed rats and a similar effect is caused by glutamine supply. In the latter, the results could be related with the described high cysteine levels related to decreased body weight (Hoffer, 1990), but we have no explanation

for the results of cafeteria-fed rats when saline solution is added. Threonine is one of the amino acids that is more absorbed in the cafeteria-diet-fed than in reference-diet-fed rats (Esteve *et al*, 1993). Addition of excess threonine to the diet is reflected in elevated plasma levels (Patten, 1988). Thus, the increased availability of threonine observed in rats fed the cafeteria diet is the result of an increased dietary intake. The higher threonine levels in rats force-fed glutamine is the result of the sustained depression of liver serine (threonine) dehydratase activity seen in pups force-fed this glutamine solution (Salvadó and Arola, 1992b) and is in agreement with the non-concentrative transport of threonine to liver cells (Fafournoux *et al*, 1990). Many changes with age are due to a peak on d 20, this day being considered the peak of lactation (Arola *et al*, 1982) and the values found here, for example, in tyrosine, are related to the values found in the literature (Remesar *et al*, 1980).

When an essential amino-acid mixture was added to the cafeteria diet, an additive effect was shown, pups grew even more (Salvadó and Arola, 1992a), less nitrogen was excreted (Salvadó and Arola, 1992a), and amino acids were more available (Salvadó and Arola, 1993) than when the cafeteria diet is administered alone. Conversely, higher nitrogen excretion was shown in chow-fed pups when they were force-fed glutamine (Salvadó and Arola, 1992b), but these changes were not observed in the deeply modified nitrogen metabolism by the cafeteria diet (Salvadó and Arola, 1992b). The present changes observed in plasma amino-acid concentrations by glutamine supplying are dependent of the diet eaten by the pups; there are differences in handling of glutamine supplied by cafeteria-diet-fed or reference-diet-fed rats and a major effect of diet over force-feeding is postulated. However, the body-weight of pups are decreased in both diets when glutamine solution is supplied, which reinforces the

statement that the mechanisms underlying the development of obesity did not run in parallel to those affecting the control of amino-acid utilization (Rafecas *et al*, 1993). On the other hand, the differences in nitrogen management caused by both diet and force-feeding may be explained by a differential control of intestinal absorption of nutrients caused by their different proportions. These changes in enteral metabolism will be translated to hepatic and overall metabolism.

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