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Impairment of arginine metabolism in rats after massive intestinal resection: effect of parenteral nutrition supplemented with citrulline compared with arginine

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ABSTRACT

Arginine homoeostasis is impaired in short bowel syndrome, but its supplementation in short bowel syndrome patients remains controversial. Recently, we demonstrated the benefits of citrulline supplementation by the enteral route in resected rats. Since the first step in managing short bowel syndrome is to initiate total parenteral nutrition, we hypothesized that parenteral citrulline supplementation would be more appropriate in this situation than arginine supplementation. In the present study, 24 rats were assigned to four groups. The sham group underwent transection whereas the three other groups underwent resection (R) of 80% of the small intestine. All rats were then fed exclusively by total parenteral nutrition as follows: supplementation with citrulline (R + CIT), with arginine (R + ARG) or no supplementation (R). All of the rats received isocaloric and isonitrogenous nutrition for 4 days. Nitrogen balance was measured daily. Rats were then killed and the blood was collected and the intestinal mucosa and extensor digitorum longus muscle were removed for amino acid and protein analysis. Citrulline and arginine increased mucosal protein content in the ileum (compared with sham and R, $P < 0.05$). However, only citrulline prevented extensor digitorum longus atrophy (R + CIT, 130 ± 3 mg compared with R, 100 ± 6 mg and R + ARG, 110 ± 2 mg, $P < 0.05$). In addition, arginine worsened nitrogen balance (R + ARG, 104 ± 46 mg/72 h compared with R, 249 ± 69 mg/72 h, $P < 0.05$). Only citrulline was able to prevent muscle atrophy and it was achieved independently from any noticeable effect on the gut in particular because citrulline and arginine share the same effect on mucosal ileal protein content. These results suggest that citrulline should be considered as a potential supplement for total parenteral nutrition of short bowel syndrome patients.

INTRODUCTION

ARG (arginine) presents numerous metabolic functions as a precursor of NO, agmatine, proline, polyamines and creatine [1]. Furthermore, ARG stimulates hormone secretion (i.e. insulin and growth hormone) [2]. Finally, it plays a key role in nitrogen homoeostasis through the control of ureagenesis [3].

Key words: arginine, citrulline, intestinal adaptation, malnutrition, short bowel syndrome.

Abbreviations: AA, amino acid; ARG, arginine, CIT, citrulline, EDL, extensor digitorum longus; R + ARG, resected supplemented with ARG; R + CIT, resected supplemented with CIT; SBS, short bowel syndrome.

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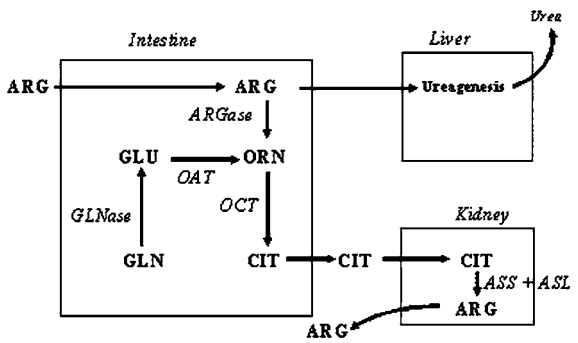

Figure 1 Intestinal-renal axis of arginine metabolism

ARGase, arginase; *ASS + ASL*, argininosuccinate synthetase + lyase; *GLNase*, glutaminase; GLU, glutamate; *OAT*, ornithine aminotransferase; *OCT*, ornithine carbamoyltransferase.

ARG homoeostasis results from tight co-operation between the intestine and the kidneys, and CIT (citrulline) has a central role in this homoeostatic process. At whole-body level, the intestine is the main site of CIT production because it is the only tissue that contains all of the enzymes required to synthesize CIT from either ARG or GLN (glutamine; see Figure 1) [4]. The kidneys (which express argininosuccinate synthase and argininosuccinate lyase) extract approx. 75 % of plasma CIT, which represents 83 % of the CIT released by the gut [5–8].

These metabolic considerations explain why SBS (short bowel syndrome) is characterized by profound perturbations of ARG metabolism [5] and why some authors [9,10] have suggested that ARG is in fact an essential amino acid in SBS. However, we previously demonstrated [11] that CIT supplementation is more efficient than ARG in increasing ARG pools and restoring nitrogen balance after massive intestinal resection in rats. In our previous work, CIT was administered by an enteral route. Since the liver and the intestine play a major role in ARG metabolism, it may be hypothesized that the route of administration (i.e. the parenteral route, which bypasses the splanchnic area, compared with the enteral route) may profoundly affect the metabolism of the administered CIT and ARG. The effect would probably be more pronounced on ARG than CIT, which is neither metabolized in the gut nor taken up or released by the liver [1,3]. The aim of the present study was to evaluate the effects of CIT and ARG administered by the parenteral route in a rat model of massive intestinal resection.

MATERIALS AND METHODS

Chemicals

All chemicals were purchased from Sigma. CIT was a gift from Biocodex (Compiègne, France).

Animals

Male Wistar rats ($n = 24$, body weight 220–230 g) purchased from Charles River were housed in metabolic cages for a 5 day acclimatization period before surgery, and were given free access to standard laboratory chow (17 % protein, 3 % fat, 59 % carbohydrate, 21 % water, vitamins and minerals) (A04, Usine d'Alimentation Rationnelle, Villemoisson-sur-Orge, France) and water.

Surgical procedures

The animals were fasted for 12 h before surgery. They were anaesthetized by isoflurane inhalation (3 % isoflurane) using a regulated airflow apparatus (Minerve). Enterectomy was performed on the rats by removing 80 % of the small intestine, leaving 10 % of the proximal jejunum and 10 % of the distal ileum, as previously described [11]. Six rats were sham-operated (transection). For both resected and transected animals, continuity was restored with end-to-end anastomosis using a single running silk 6-0 suture. Immediately after intestinal resection or transection, a catheter was fitted into the jugular vein. A silicone tube (Tygon, size 0.51 mm, Fisher Bioblock Scientific) was introduced into the vein and the remaining end of the catheter was tunnelled subcutaneously to the back of the neck and attached to a spring coil-swivel mechanism (Harvard Apparatus) allowing the rats to move freely within the cage [12,13].

Before the surgical procedure, all the rats received a painkiller (Temgesic®; Schering-Plough) subcutaneously at a dose of 0.05 mg/kg of body weight.

Animal care complied with French regulations for the protection of animals used for experimental and other scientific purposes (D 2001-486) and with European Community regulations (Official Journal of the European Community L538 12:18:1986).

Post-operative care

The rats were housed individually in metabolic cages. Parenteral nutrition was started immediately after surgery. Parenteral nutrition was given using a Harvard infusion pump (Pump 11, Harvard Apparatus). During the first 24 h of parenteral nutrition, the flow rate was increased progressively to reach a final rate of 300 ml/kg of body weight per day, which corresponds to a nitrogen intake of 2 g/kg of body weight per day and energy intake of 260 kcal/kg of body weight per day, covering the nutritional requirements in rats [11–13]. The rats had free access to water.

Experimental groups

The rats were randomly assigned to one of four groups: (i) in the citrulline group [R (resected) + CIT, $n = 6$], the rats received standard parenteral nutrition (Vintène®, Baxter) (Table 1) supplemented with CIT at a dose of 1 g/kg of

Table 1 Composition of the amino acid solution (mmol/l)

Amino acid	
Essential amino acids	
L-Isoleucine	53
L-Leucine	107
L-Valine	60
L-Lysine	68
L-Phenylalanine	55
L-Methionine	47
L-Threonine	46
L-Tryptophan	12
Non-essential amino acids	
L-Aspartate	23
L-Serine	29
L-Glutamate	34
L-Proline	96
Glycine	123
L-Alanine	146
L-Histidine	26
L-Arginine	86
L-Tyrosine	2
L-Cysteine hydrochloride	13
L-Ornithine hydrochloride	8

body weight per day (5.71 mmol/kg of body weight per day); (ii) in the arginine group (R + ARG, $n = 6$), the rats received the standard parenteral nutrition supplemented with ARG at a dose of 0.994 g/kg of body weight per day, making it equimolar to the R + CIT group; (iii) in the control group (R, $n = 6$) and (iv) in the sham group (sham, $n = 6$), the rats received standard parenteral nutrition and were either resected (R) or transected (sham).

In all groups, energy was supplied as carbohydrate (glucose 50 %) and long-chain triacylglycerols containing fat emulsion (Endolipid 20 %; B. Braun Medical). The nutritional regimen also provided electrolytes (Standard III, Aguettant) and water. All of the groups received isonitrogenous (2 g nitrogen/kg of body weight per day, adjusted adding Vintene® in R, sham and R + CIT groups) and isocaloric (260 kcal/kg of body weight per day) nutrition. Nitrogen and calorie intakes and amounts of CIT or ARG mimicked those used in clinical nutrition, which takes into account the fact that metabolic rate is 10-fold higher in rats than in humans [11,14,15].

The rats were weighed and urine was collected daily. Total parenteral nutrition was administered for 4 days. Parenteral nutrition was stopped 2 h before rats were killed by decapitation.

Tissue removal

Blood was collected into heparinized tubes, which were rapidly centrifuged.

The intestine was resected from the ligament of Treitz to the ileocaecal junction. The mucosa was washed with 0.9 % NaCl, everted and scraped off, and then weighed and rapidly frozen in liquid nitrogen and stored at − 80 °C until analysis.

The EDL (extensor digitorum longus) muscle was rapidly removed, weighed, and then frozen in liquid nitrogen and stored at − 80 °C until analysis.

Parameters under study and analytical methods

AA (amino acid) concentrations in plasma and tissues were analysed. Plasma was deproteinized with a 30 % (w/v) sulfosalicylic acid solution and the supernatants were stored at − 80 °C until analysis. Tissues were ground and deproteinized with 10 % TCA (trichloroacetic acid) containing 0.5 mM EDTA, and the supernatants were stored at − 80 °C until analysis. AAs were measured by ion-exchange chromatography [16] using an amino acid analyser (AminoTac, JLC-500/V, Jeol). The results of our participation in the European Quality Control Scheme (ERNDIM, Maastricht, The Netherlands) indicate the accuracy of our AA determinations.

To analyse polyamines, dansyl derivatives of intestinal polyamines were assayed according to the method of Seiler and Knodgen [17], with some modifications. Intestine samples were homogenized in a phosphate-buffer (50 mM KH_2PO_4/Na_2HPO_4, 300 μl of buffer per mg of tissue). Homogenates were centrifuged for 5 min at 3000 ***g***. Supernatants were diluted 15 times in phosphate buffer and stored at − 80 °C until analysis. Samples were incubated for 2 h at 60 °C in the dark with 0.5 ml of dansyl chloride (5 mg/ml in acetone). The solution was then evaporated under nitrogen and extraction was performed using 8 ml of 30 % (v/v) methanol. The organic phase was collected and evaporated, and the dansyl derivatives were resuspended in 0.1 ml of the initial mobile phase and 20 μl were injected into the chromatograph. Dansylputrescine, dansylspermidine and dansylspermine were separated on a C_8 column (length: 15 cm, particle diameter: 5 μm) using the 5500 Vista Varian pump system (Varian). After fluorimetric detection, polyamine concentrations were estimated by the internal standard method (the standard used was hexanediamine). Results are expressed as nmol/g of tissue.

Nitrogen was quantified by chemiluminescence [18] using an Antek 9000 apparatus (Antek), and nitrogen balance was calculated as the difference between nitrogen intake and urinary nitrogen output.

Statistical analysis

Values are expressed as means ± S.E.M. Comparisons between sets of data were made using ANOVA followed by the Duncan test. PCSM software was used (Deltasoft). Differences at $P < 0.05$ were considered significant.

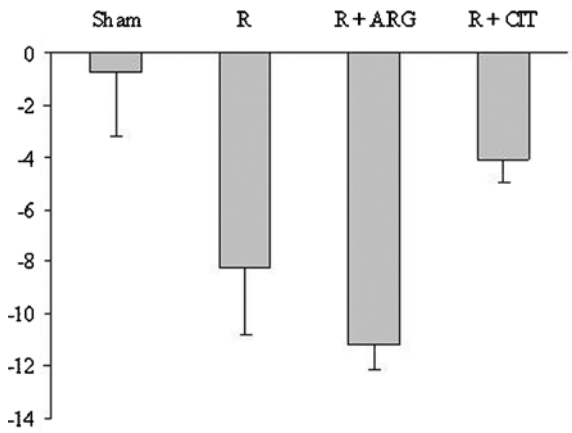

Figure 2 Cumulative body weight loss over the duration of total parenteral nutrition (g)

Four groups of rats were studied: sham (transected rats fed standard parenteral nutrition), R (resected rats fed standard parenteral nutrition), R + ARG (resected rats fed an ARG-supplemented formula), R + CIT (resected rats fed a CIT-supplemented formula). Values are expressed as means ± S.E.M.

RESULTS

Body weight loss (Figure 2) (i.e. the difference between body weight at the beginning of total parental nutrition administration and the end of the experiment) did not differ significantly in the four study groups.

The muscle and intestinal mucosa weights are shown in Table 2. Gut resection led to muscle atrophy (R compared with sham, $P < 0.05$). However, EDL weight was restored by CIT supplementation (R + CIT compared with R and R + ARG, $P < 0.05$). ARG and CIT supplementation increased mucosal ileum weight (R + CIT and R + ARG compared with sham, $P < 0.05$) whereas only the CIT-treated group had a higher mucosal jejunum weight than sham (R + CIT compared with sham, $P < 0.05$).

Table 2 shows the protein content in the intestinal mucosa and EDL muscle. There were no significant changes in the protein content in EDL muscle. Intestinal resection led to a significant increase in mucosal protein content in the jejunum (R compared with sham, $P < 0.05$) without a significant additional effect of ARG or CIT supplementation. The mucosal protein content of the ileum, which was not modified by resection, was significantly increased in both the ARG- and CIT-supplemented groups (R + ARG and R + CIT compared with sham and R, $P < 0.05$).

With regards to amino acid concentrations, CIT was the only amino acid whose profile was influenced by resection or by the different diets (Table 2).

In plasma, intestinal resection led to a decrease in CIT levels compared with the sham group (R compared with sham, $P < 0.05$). CIT administration led to an increase in plasma CIT concentrations (R + CIT compared with sham, R and R + ARG, $P < 0.05$). In the CIT group, the

Table 2 Muscle and intestinal weight, protein content, CIT concentration and ARG concentration in the four groups of rats

Four groups of rats were studied: sham (transected rats fed standard parenteral nutrition), R (resected rats fed standard parenteral nutrition), R + ARG (resected rats fed an ARG-supplemented formula) and R + CIT (resected rats fed a CIT-supplemented formula). Values are expressed as means ± S.E.M. Values in a row with superscript letters are statistically different at $P < 0.05$ (measured using ANOVA and Duncan's test).

Measurement	Sham	R	R + ARG	R + CIT
Muscle and intestinal mucosa weight				
EDL (mg)	$120 \pm 6^{a,c}$	100 ± 6^{b}	$110 \pm 2^{a,b}$	130 ± 3^{c}
Jejunum (mg/cm)	36 ± 6^{a}	$48 \pm 6^{a,b}$	$52 \pm 3^{a,b}$	65 ± 9^{b}
Ileum (mg/cm)	26 ± 2^{a}	$44 \pm 5^{a,b}$	54 ± 3^{b}	52 ± 9^{b}
Protein content in the intestinal mucosa and EDL muscle				
EDL (mg)	11.9 ± 1.9	10.1 ± 1.4	11.9 ± 0.9	13.6 ± 0.8
Jejunum (mg/g)	46 ± 3^{a}	57 ± 7^{b}	72 ± 4^{b}	73 ± 6^{b}
Ileum (mg/g)	51 ± 3^{a}	53 ± 7^{a}	71 ± 5^{b}	72 ± 3^{b}
CIT concentration in plasma and tissues				
Plasma (μmol/l)	80 ± 6^{a}	46 ± 2^{b}	41 ± 5^{c}	114 ± 7^{d}
EDL (nmol/g)	167 ± 16^{a}	79 ± 7^{b}	100 ± 16^{c}	502 ± 27^{d}
Jejunum (nmol/g)	145 ± 25^{a}	59 ± 10^{b}	63 ± 17^{c}	143 ± 33^{a}
Ileum (nmol/g)	141 ± 35	53 ± 13	86 ± 21	156 ± 37
ARG concentration in plasma and tissues				
Plasma (μmol/l)	246 ± 24	228 ± 31	244 ± 25	288 ± 19
EDL (nmol/g)	1200 ± 163	1071 ± 204	951 ± 122	1131 ± 184
Jejunum (nmol/g)	304 ± 63	444 ± 80	467 ± 66	200 ± 61
Ileum (nmol/g)	200 ± 58	401 ± 113	256 ± 62	190 ± 31

Table 3 Polyamine content in the intestinal mucosa

Four groups of rats were studied: sham (transected rats fed standard parenteral nutrition), R (resected rats fed standard parenteral nutrition), R + ARG (resected rats fed an ARG-supplemented formula), R + CIT (resected rats fed a CIT-supplemented formula). Values are expressed as means ± S.E.M. Values in a row with superscript letters are statistically different at $P < 0.05$ (measured using ANOVA and Duncan's test).

Polyamine	Sham	R	R + ARG	R + CIT
Jejunum				
Putrescine	55 ± 14	89 ± 11	70 ± 12	84 ± 14
Spermidine	697 ± 62[a]	1004 ± 46[b,c]	821 ± 57[a,c]	987 ± 100[b,c]
Spermine	401 ± 20	520 ± 25	392 ± 33	444 ± 67
Ileum				
Putrescine	44 ± 4	68 ± 29	128 ± 23	86 ± 28
Spermidine	879 ± 87	951 ± 20	1048 ± 80	909 ± 131
Spermine	614 ± 27	526 ± 73	479 ± 29	499 ± 78

increase in EDL weight was positively correlated with plasma CIT concentration ($r = 0.73$, $P < 0.0001$).

In muscles, intestinal resection led to a decrease in muscle CIT levels (R compared with sham, $P < 0.05$). Only CIT supplementation led to a significant increase in muscle CIT levels (R + CIT compared with sham, R and R + ARG, $P < 0.05$).

In intestinal mucosa, after intestinal resection, there was a decrease in CIT content in the mucosal jejunum (R compared with sham, $P < 0.05$). Although both CIT and ARG led to an increased CIT content in the mucosal jejunum, only CIT supplementation was able to completely restore mucosal jejunum CIT content (R + CIT compared with R and R + ARG, $P < 0.05$).

There were no treatment effects on ARG levels (Table 2) or on other AAs (results not shown).

Table 3 shows the polyamine content in intestinal mucosa. Intestinal resection was associated with a significant increase in spermidine (R compared with sham, $P < 0.05$). This higher level of spermidine content was also found in the mucosal jejunum from the CIT-supplemented group (R + CIT compared with sham, $P < 0.05$) but not in the ARG-supplemented group (R + ARG compared with sham, not significant). There was no difference in spermine or putrescine contents between the groups studied.

The nitrogen balance is shown in Figure 3. Cumulative nitrogen balance was significantly lower in the three resected groups compared with the sham group (sham compared with R, R + ARG and R + CIT, $P < 0.05$), especially when the diet was supplemented with ARG (R + ARG compared with R, $P < 0.05$).

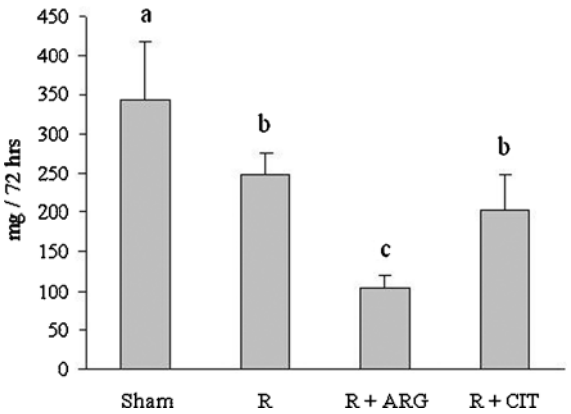

Figure 3 Nitrogen balance over the duration of total parenteral nutrition (mg/72 h)

Four groups of rats were studied: sham (transected rats fed standard parenteral nutrition), R (resected rats fed standard parenteral nutrition), R + ARG (resected rats fed an ARG-supplemented formula), R + CIT (resected rats fed a CIT-supplemented formula). Results are expressed as the difference between daily nitrogen intake and daily urinary nitrogen excretion. Values are expressed as means ± S.E.M. Values with different superscript letters are statistically different at $P < 0.05$ (measured using ANOVA + Duncan's test).

DISCUSSION

The intestine is an important organ for the maintenance of ARG homoeostasis and therefore for whole-body nitrogen homoeostasis. The pioneering study by Crenn et al. [19] together with earlier experimental data [9,10] suggest that ARG administration could become critical in SBS. In fact, the metabolic specificities of ARG and its related AAs (see Introduction) together with our previous study [11] show that it is CIT administration rather than ARG administration which could be a better strategy in an SBS setting.

As expected, there was a 2-fold increase in plasma CIT concentrations after parenteral CIT administration. This result is in agreement with our previous work using enteral infusion [11]. However, CIT supplementation did not affect the ARG concentration in either the plasma or in the tissues. This is a surprising result since we previously observed that the same amount of CIT (i.e. 1 g/kg of body weight per day) given by an enteral route is able to generate a large amount of ARG in resected animals [11]. The main factor determining ARG synthesis by the kidney is plasma CIT concentration [6]. Since renal function, assessed on the basis of urinary creatinine, was not altered in our model (results not shown), it is likely that ARG synthesis was not compromised. Previous studies [5,7,8] indicate that ARG catabolism is the main regulator of ARG homoeostasis. Using a similar model of enterectomy and labelled isotopes, Dejong et al. [20] demonstrated that net renal CIT uptake and ARG release were both decreased by 50% owing to intestinal resection. However, despite decreased net renal CIT consumption and renal ARG production in enterectomized rats, neither the whole-body rate of ARG appearance nor arterial ARG were modified, prompting the same group [21] to conclude that intestinal resection

does not have important effects on whole-body ARG production. Therefore our results clearly show that ARG administration failed to increase ARG pools. The dosage used cannot be questioned since the same dose (0.994 g/kg of body weight per day) given by an enteral route in the same SBS rat model was associated with a large increase in plasma and muscle ARG content [11]. This suggests that ARG is intensively metabolized in response to intestinal resection and that ARG metabolism is clearly affected by the route of administration {sham + standard enteral nutrition: ARG, 110 ± 12 μmol/l (from [11]) and sham + standard parenteral nutrition: ARG, 246 ± 24 μmol/l}. This may reflect the importance of splanchnic first-pass in ARG metabolism. However, the time schedule of the present study was different from our previous study [11] and so comparison of results requires caution. The few results available on parenteral supplementation in SBS rats [21,22] actually did not use the same route of administration (i.e. ARG was administered subcutaneously, which does not reflect an intravenous administration). Another explanation is that the rats were studied earlier than in our previous study [11], making the rats more catabolic with a higher ARG turnover. Finally, in certain pathological situations, the liver appears to be able to extract CIT [23,24] by diverting this AA from kidney capture. The results were obtained using the enteral route [11], and the parenteral route shows that CIT reaching the liver by the arterial artery has a different behaviour from CIT coming from the portal vein. This point deserves further study. Furthermore, studies using labelled AAs and arterio-venous difference measurements are required to define ARG use at whole-body and organ levels, following resection.

Our results suggest that ARG and CIT increase mucosal weight and mucosal protein content. We also observed that these effects could differ according to the intestinal section (jejunum or ileum). This difference may be related to differences in the adaptation process that are not yet understood. These results are promising, which suggest that CIT and ARG could affect gut protein content. It would be interesting to extend our investigation to specific markers of intestinal adaptation (i.e. bowel circumference, bowel weight, mucosa DNA content, villus height and crypt depth) and to determine the mechanism involved in this action. The effect of ARG on intestinal adaptation remains controversial [9,10,20,22,25,26]. At the molecular level, the synthesis of intracellular polyamines is a critical event for the onset of mucosal hyperplasia. Hence, these molecules play an important role in the maintenance of intestinal mucosa [27]. This is well illustrated in SBS, since a significant increase in the polyamine content of the remaining intestine has been reported previously [20,28]. However, in the present study, only spermidine was increased in the jejunum (R and R + CIT compared with sham, $P < 0.05$). This discrepancy with the literature may be because polyamine content usually increases in the first hours following resection (less than 24 h) [29,30]. In the present study, polyamine assays were performed 96 h after resection, and the absence of the significantly increased polyamine content after this period is consistent with the studies cited above.

Alternatively ARG, when given parenterally, may be used preferentially by other tissues. As expected, resected animals exhibited a decreased nitrogen balance. Although CIT had no effect on nitrogen balance, ARG clearly appeared to have a deleterious effect. This could be explained as follows: as arginase activity is very high in the liver [31], most of the ARG that reaches the liver is converted into urea. This fact was well illustrated by the study of De Bandt et al. [32] in a model of isolated perfused liver. These authors demonstrated that ARG was extensively taken up by the liver and rapidly released as ORN (ornithine) and urea, which supports ARG-induced acceleration of AA catabolism and activation of the urea cycle. However, CIT, which is not taken up by the liver [33], limits the activation of ureagenesis, making it a candidate therapy for preserving nitrogen balance. However, the present study using parenteral administration did not reproduce the beneficial effect of CIT on nitrogen balance observed when CIT is administered by enteral nutrition [11]. As for the ARG levels, this discrepancy may be explained by the difference in the duration of the treatment (3 days in the present study compared with 10 days in [11]), because the beneficial effect of CIT was observed only after the fourth day of treatment.

Finally, EDL weight was increased in the CIT-supplemented group compared with both the control and ARG-supplemented groups. Interestingly, this increase was positively correlated with plasma CIT concentrations ($r = 0.73$, $P < 0.0001$). This unexpected finding could be related to the ability of CIT to stimulate muscle protein synthesis [34]. We recently showed [35] that CIT administration to malnourished old rats stimulates muscle protein synthesis, which could explain the trend in increased muscle protein content observed in the present study. In addition, our recent research [36] using isolated incubating muscles suggests that CIT is able to directly affect protein synthesis. However, to the best of our knowledge, our work is pioneering and there are no results available in the literature that might help us to explain this effect. Alternatively, a modification of water content might be involved. Unfortunately, this variable was not measured in the present study. However, we previously measured muscle water content in a number of studies in several physiopathological conditions (aging, enteral or parenteral nutrition, stress, malnutrition, SBS, etc.) and it was never modified by treatment. The present work does not enable us to draw definitive conclusions: further work to assess body composition (using DEXA or ^2H_2O methods), whole body and tissues protein synthesis would help to determine the precise influence of CIT on lean body mass in various tissues and organs.

In conclusion, parenteral CIT supplementation restores the plasma CIT pools that are reduced after intestinal resection. However, our results are different from those obtained after enteral administration. This suggests that the route of administration (i.e. enteral compared with parenteral) has profoundly different effects on ARG metabolism. CIT shares with ARG the positive effect on intestinal adaptation in terms of intestinal mucosa weight and protein content. However, only CIT also has a positive effect on muscle weight and importantly, ARG administration worsens nitrogen balance, whereas CIT does not. These results suggest that CIT could be potentially considered as a supplement in parenteral nutrition for the patients with SBS in order to preserve nutritional state and promote intestinal adaptation. Together with our previous work [11], these results open the way to clinical trials in patients suffering from SBS.

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