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Plasma arginine correlations in trauma and sepsis

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Summary. Arginine (ARG) is an amino acid (AA) with unique properties and with a key-role in the metabolic, immune and reparative response to trauma and sepsis. This study has been performed to characterize the correlations between plasma levels of ARG, of other AA and of multiple metabolic variables in trauma and sepsis.

Two-hundred and sixty-three plasma amino-acidograms with a large series of additional biochemical and blood variables were obtained consecutively in 9 trauma patients who developed sepsis, undergoing total parenteral nutrition with dextrose, fat and a mixed AA solution containing 10.4% arginine.

ARG was low soon after trauma, then it increased with increasing distance from trauma and with the development of sepsis. ARG was also directly related to the AA infusion rate (AAIR) and for any given AAIR, was lower after trauma than after the development of sepsis. ARG was also related directly to the plasma levels of most of the other AA, the best correlation being that with lysine ($r^2 = 0.81$, $p < 0.001$). These correlations were often shifted downwards (showing lower ARG for any given level of the other AA) in measurements performed after trauma, compared to those performed after development of sepsis; this effect was more pronounced for the correlations with branched chain AA. Correlations between ARG and non-AA variables were not particularly relevant. The best simultaneous correlates of ARG, among variables involved in plasma ARG availability, were citrulline level, AAIR and urinary 3-methylhistidine excretion (accounting for the effect of endogenous proteolysis) (multiple $r^2 = 0.70$, $p < 0.001$). Plasma ornithine (ORN), the AA more specifically linked to ARG metabolism, correlated with AAIR better than ARG and, for any given AAIR, was lower after trauma than after the development of sepsis. Correlations of ORN with other AA levels were poorer than those found for ARG, however ORN was directly related to white blood cell and platelet count, fibrinogen, transferrin, cholesterol and many AA clearances.

These data show that changes in ARG in trauma and sepsis are correlated with changes in other AA and, within these correlations, reconfirm a tendency to lower ARG in trauma compared to sepsis. The strong correlation with lysine warrants a deeper assessment of the practical implications of interdependency between these two AA. The data also suggest that changes in plasma ORN in trauma and sepsis may reflect adequacy of AA substrate to support acute-phase and other synthetic processes.

Keywords: Plasma arginine – Amino acids – Sepsis – Parenteral nutrition – Ornithine – Branched chain amino acids

Introduction

Arginine (ARG) is an amino acid (AA) with unique properties. Besides being a major nitrogen carrier and a component of proteins, it is a precursor for the synthesis of molecules with enormous biological importance, including urea, ornithine, polyamines, nitric oxide, creatine, agmatine and many others (Ochoa et al., 1991, 2004; Zaloga et al., 2004; Flynn et al., 2002; Suchner et al., 2002; Grillo and Colombatto, 2004a, b; Satriano, 2004; Rodriguez, 2003; Stechmiller et al., 2005). After surgery, in other post-traumatic states and in sepsis it is also known to take an active part in the maintenance of immune function, host defense, inflammatory processes, wound healing, and in a series of pathophysiologic adaptations (Ochoa et al., 1991, 2004; Zaloga et al., 2004; Wu and Morris, 2004; Abumrad and Barbul, 2004). In spite of the key-role of ARG in these conditions, the correlations between its plasma levels and those of other amino acids and plasma variables have never been systematically characterised. This study was performed to obtain a detailed quantitative assessment of these relationships in patients with trauma and sepsis.

Materials and methods

The study was performed on data collected prospectively on nine severely injured trauma patients (3 women, 6 men) who developed sepsis. Median age was 25 years (range 17–38), weight was 70 Kg (40–85), height 170 cm (163–188), injury severity score 31 (14–48) (Greenspan et al., 1985). The patients had a combination of abdominal, chest and head injuries, and cause of sepsis was intraabdominal, pulmonary or extensive soft tissue infection. Serial measurements were performed every 8 to 12 hours after patient admission, and continued during sepsis until the clinical

Table 1. Composition of the infused AA solution in g and in mmol per 100 g total AA

AA	g/100 g AA	mmol/100 g AA
ALA	20.7	232.4
ARG	10.4	59.4
GLY	20.7	275.8
HIS	4.4	28.2
ILE	4.8	36.4
LEU	6.2	47.2
LYS	5.8	39.6
MET	5.8	38.8
PHE	6.2	37.4
PRO	4.2	36.4
THR	4.2	35.1
TRP	1.8	8.8
TYR	0.4	2.2
VAL	4.6	39.1

criteria for the diagnosis of sepsis persisted, for a total of 263 measurements. The diagnosis of sepsis was based on the simultaneous occurrence of a temperature >38.3 °C, white blood cell count $>12 \times 10^9$/L or $<3 \times 10^9$/L and clear evidence of infection confirmed by positive cultures from blood, surgical drainage of infected areas or sputum in the case of pulmonary sepsis. Median sepsis severity score (Skau, 1985) upon diagnosis of sepsis was 25.5 (range 11–75). One patient died of progressive septic metabolic decompensation with multiple organ dysfunction syndrome, the remainder survived. The patients were receiving total parenteral nutrition (34 ± 7 kcal/kg/day, 76% glucose and 24% fat, and 1.6 ± 0.5 g/kg/day mixed amino acids) (composition of the AA solution in Table 1). Each measurement included the full amino-acidogram and the levels of plasma albumin, ceruloplasmin, C-reactive protein, alpha-2-macroglobulin, alpha-1-antitrypsin, fibrinogen, transferrin, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, cholesterol, triglycerides, alkaline phosphatase, lactate, blood cell count, an estimation of plasma AA clearances (Clowes et al., 1980a, b) and daily 3-methylhistidine and urea excretion. Data were reported as medians with 10% and 90% percentiles. The statistical analysis and validation of the results were performed by least-square regression and covariance analysis, with skewness and kurtosis control, and analysis of residuals (Statgraphics Plus, Manugistics, Rockville, MD). Significance of covariance was assessed by Scheffé criteria (based on confidence intervals and differences in slope and intercept) and Mallows' Cp criteria, to select for each correlation the simplest possible regression yielding the best control of variability (Seber, 1977). The protocol complied with the Helsinki declaration as revised in 1983, and was approved by the Institutional Ethical Committee.

Results

Plasma ARG level for the whole group of measurements was 99.5 (median; 10%–90% percentiles 70–172) (Table 2). The standard reference range was 69–101 μmol/L. Plasma ARG was low immediately after trauma (68; 29–89), thereafter it increased with increase in both distance from trauma and exogenous AA support ($p < 0.01$ for both). At the time of diagnosis of sepsis ARG was 87; 41–175. Regression analysis on all measurements showed that ARG was directly and significantly related to amino acid infusion rate (AAIR, g/kg/day) ($r^2 = 0.20$, $p < 0.001$), and unrelated to the infusion rate of other substrates. It was strongly related to the plasma levels of most of the other AA: there was a best linear direct correlation with LYS ($r^2 = 0.81$, $p < 0.001$), and

Table 2. Medians with 10% and 90% percentiles for plasma AA and other variables considered in the study

Variable	Median (10% and 90% percentiles)
ABU (μmol/L)	15 (9–44)
ALA (μmol/L)	335 (201–646)
ARG (μmol/L)	99.5 (70–172)
ASN (μmol/L)	50 (25–183)
ASP (μmol/L)	7 (3–14.5)
β-ALA (μmol/L)	6 (4–11.5)
CIT (μmol/L)	12 (7–31)
CYS-CYS (μmol/L)	44 (29–78)
GLN (μmol/L)	458 (356–811)
GLU (μmol/L)	53 (19–125)
GLY (μmol/L)	311 (181–525)
HIS (μmol/L)	83 (60–147)
HYP (μmol/L)	12.5 (6–30)
ILE (μmol/L)	67 (39–95)
LEU (μmol/L)	121 (90–199)
LYS (μmol/L)	187 (128–310)
MET (μmol/L)	48 (29–157)
ORN (μmol/L)	88 (49–175)
PEA (μmol/L)	8 (3–19)
PHE (μmol/L)	126 (96–233)
PRO (μmol/L)	227 (150.5–853.5)
SER (μmol/L)	107 (71–158)
TAU (μmol/L)	64 (25–139)
THR (μmol/L)	119 (76–278)
TRP (μmol/L)	57 (37–76)
TYR (μmol/L)	61 (41–108)
VAL (μmol/L)	236 (179–382)
Albumin (g/dL)	2.4 (1.8–2.9)
Ceruloplasmin (μg/mL)	482 (292–622)
C-reactive protein (μg/mL)	205 (96–330)
α-2-macroglobulin (mg/mL)	2.01 (1.38–3.13)
α-1-antitrypsin (mg/mL)	6.78 (2.15–10.20)
Fibrinogen (mg/mL)	8.96 (5.42–13.30)
Transferrin (mg/mL)	1.60 (0.96–2.10)
Glucose (mg/dL)	128 (108–190)
Blood urea nitrogen (mg/dL)	21 (11–41)
Creatinine (mg/dL)	0.8 (0.5–1.7)
Sodium (mEq/L)	140 (132–155)
Potassium (mEq/L)	4.1 (3.4–4.8)
Chloride (mEq/L)	103 (95–112)
Calcium (mg/dL)	7.8 (7.1–8.7)
Cholesterol (mg/dL)	81.5 (53–129)
Triglycerides (mg/dL)	207 (93–344)
Alkaline phosphatase (U/L)	110 (63–209)
Lactate (mg/dL)	14.8 (9.5–34.4)
Hemoglobin (g/dL)	10.9 (9.9–12.1)
WBC count (10^9/L)	16.8 (8.5–28.7)
Platelet count (10^9/L)	285 (74–512)
3-methylhistidine excretion (μmol/24 h)	588 (299–967)
Urea excretion (g/24 h)	22.6 (11.1–38.4)

other direct correlations with SER, THR, GLY, ILE, ALA, LEU, GLN, PRO, VAL, ABU (r^2 = from 0.72 to 0.50, $p < 0.001$ for all) and with CIT, HIS, ORN, ASP, ASN, HYP, PHE and TYR ($r^2 = 0.45$ to 0.30, $p < 0.001$ for all). ARG was more weakly related, or unrelated, to other AA. The highest ARG levels (>172 μmol/L, or >90% percentile) were observed in patients with extreme septic illness, hyperlactatemia and signs of multiple organ failure, in concomitance with largely increased levels of most of the related AA. Plasma ARG levels were lower after simple trauma than after the development of sepsis (90, 66–153 vs. 102, 72–181, $p < 0.03$). The direct relationship between ARG and the previously listed AA was also observed by separately evaluating measurements performed before or after the development of sepsis, however in the former group this relationship was frequently shifted downward (lower ARG for any given value of the other AA). This effect often reached significance, and was particularly amplified for the relationships between ARG and LEU, VAL or ILE ($p < 0.001$, Table 3 and Fig. 1). Strength and shape of the relationships was equivalent for each of these three AA, as their levels were closely interrelated. This was always true for LEU and VAL ($r^2 = 0.96$, $p < 0.001$) while in two patients increases of LEU and VAL were paralleled by comparably smaller increases of ILE. With this exception, there was an evident tendency for a constant VAL:LEU:ILE ratio of 3.0:1.5:1.0.

A downward shift was also observed for the relationship between ARG and AAIR after simple trauma compared to sepsis (with measurements performed after simple trauma showing lower ARG for any given AAIR, compared to those performed after the development of sepsis) ($p < 0.001$). The relationship with LYS (the best

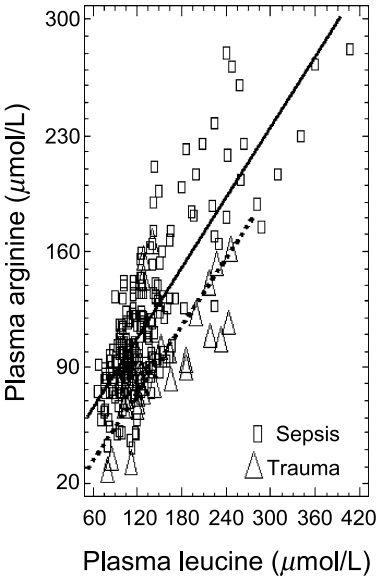

Fig. 1. Computer-generated display of the relationship between plasma arginine and leucine for measurements performed after simple trauma (triangles) or after the development of sepsis (squares). Regression lines for the former (dotted line) and the latter (continuous line) obtained from regression 1, Table 3

correlate of ARG, $r^2 = 0.81$, Table 3 and Fig. 2) remained unmodified in measurements performed before or after the development of sepsis and was not improved by the inclusion of any other variable considered in the study except the AAIR, which brought the total r^2 to 0.86 ($p < 0.001$,

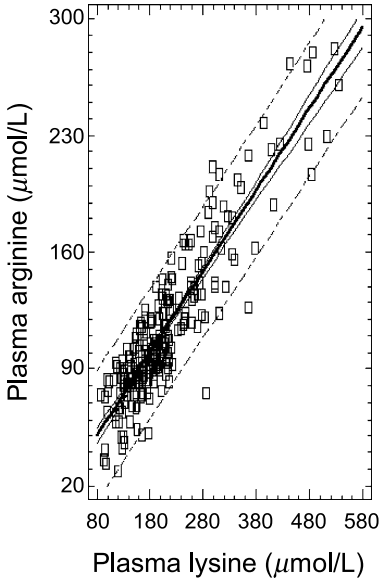

Fig. 2. Computer-generated display of the relationship between plasma arginine and lysine, with regression line and 95% confidence limits for the line and the whole distribution of measurements (from regression 2, Table 3). The relationship did not differ for measurements performed before or after the development of sepsis, symbols are unified

Table 3. Least square regressions on ARG, quantifying the relationships existing between ARG and the other variables. The coefficient before each variable is a slope estimating the mean change in ARG which is associated with a unit change in that variable. The coefficient for [TRAUMA] in regression 1 quantifies the decrease in ARG intercept associated with simple trauma (n = 35) compared to sepsis (n = 228) with unmodified slope. The r^2 values, multiplied by 100, indicate the percent of variability of ARG explained by changes in the variables included in each regression. Symbols and units as in Table 2, $p < 0.001$ for each regression and each individual coefficient

1. ARG = 0.69(LEU) − 31.88$_{[TRAUMA]}$ + 23.94	$r^2 = 0.62$, $p < 0.001$
2. ARG = 0.49(LYS) + 10.96	$r^2 = 0.81$, $p < 0.001$
3. ARG = 0.49(LYS) + 16.08(AAIR) − 13.76	$r^2 = 0.86$, $p < 0.001$
4. ARG = 2.19(CIT) + 37.41(AAIR) + 0.03(3-MeHIS)	$r^2 = 0.70$, $p < 0.001$

Table 3). Among non-AA variables there were no similarly remarkable correlations with ARG. The best simultaneous correlates, among variables accounting for factors directly involved in plasma ARG availability (endogenous synthesis, exogenous supply, proteolysis) (Flynn et al., 2002; Wu and Morris, 2004; Pita et al., 2004) were plasma CIT level, AAIR and urinary 3-methyl-histidine excretion (3-MeHIS), which together explained 70% of plasma ARG variability (Table 3). Finally the correlations with ORN, the AA more specifically linked to ARG metabolism, were also explored. ORN was not administered, but correlated with AAIR slightly better than ARG ($r^2 = 0.25$, $p < 0.001$) and for any given AAIR was lower in measurements performed before the development of sepsis ($p < 0.001$). The correlations with the other AA, however, were less strong than those observed for ARG. Detailed analysis of all measurements showed that this was because ORN in several instances followed a dissociated pattern, and failed to participate in the generalized hyperaminoacidemia which characterized the stages of more severe septic illness. In turn, ORN showed important correlations with several non-AA variables to which ARG was unrelated. These included WBC and platelet count, cholesterol, transferrin, fibrinogen, and many AA clearances (direct correlations, $r^2 > 0.30$ and $p < 0.001$ for all).

Discussion

While reconfirming several findings related to changes in plasma ARG and in other AA levels in post-traumatic states and sepsis, this study provides new relevant information on still unexplored aspects. The pattern of distribution of ARG correlations reflects the concept that, in spite of the individual properties of each AA, there is a tendency for many plasma AA levels to undergo similar patterns of change (Hjelm et al., 1993). Within this wide assessment of AA correlations, it has been possible to confirm the observation of low plasma ARG levels after trauma, and the evidence of an increased extravascular flow of ARG in this condition, also in comparison with sepsis. Indeed, in the post-traumatic state compared to the state after development of sepsis, there was a lower ARG for any given AAIR, and a downward shift in the relationship with plasma levels of other AA. This finding is consistent with an increased need for ARG after trauma, to support reparative processes and cell proliferation (Cynober, 2004; Ochoa et al., 2004; Zaloga et al., 2004; Wu et al., 2004; Abumrad and Barbul, 2004; Bistrian, 2004), and is also more remarkable if the higher concentration of ARG in the infused solution (Table 1), compared to the concentrations of other AA, is taken into account. On the other hand endogenous proteolysis seems to be a limited source of ARG, as also shown by the coefficient for 3-MeHIS in the last regression in Table 3. This coefficient, given a conversion factor of 4.2 to estimate proteolysis from urinary 3-MeHIS (Neuhäuser et al., 1980), suggests that about 80 g/day protein catabolism is needed to increase plasma ARG by 10 μmol/L.

With regard to sepsis, the issue is more complex, and also controversial (Argaman et al., 2004; Ochoa et al., 2004; Zaloga et al., 2004; Luiking et al., 2005). The possibility that increased ARG might unduly amplify nitric oxide production and inflammatory processes has long been questioned (Moncada et al., 1991; Lorente et al., 1993; Chiarla et al., 1994) and is still a cause of concern. In our study the highest ARG levels were observed in patients with extreme septic illness, hyperlactatemia and signs of multiple organ failure, in concomitance with largely increased levels of most of the other AA. This ''hyperaminoacidemia'' is a well-known feature of extreme septic metabolic decompensation (Cerra et al., 1980). Many of our measurements performed in septic patients have shown the tendency for relatively low plasma ARG and high levels of other AA (infused in lower doses than ARG), which may support the concept of an increased extravascular flow and metabolic need of ARG also in sepsis (Argaman et al., 2004). However this does not resolve the controversial issues regarding the possible overproduction of nitric oxide. An important aspect, which is frequently ignored but may help to reconcile controversies, is the circumstance that sepsis is not a unique disease: rather, in sepsis there are different stages of metabolic and cardiorespiratory decompensation (Siegel et al., 1979) in which the effect of ARG availability should be distinctly assessed in future studies. For instance, the issue may be totally different in the presence of low plasma ARG with a still compensated metabolic response, or in the presence of the high ARG with generalized hyperaminoacidemia which characterizes more severely unbalanced and often preterminal stages of septic dysmetabolic evolution (Cerra et al., 1980).

The partial dependency of ARG and ORN levels on AAIR which was observed in our study is in agreement with previously performed observations during enteral or parenteral ARG administration (Bérard et al., 2000, 2002, Preiser et al., 2001; Wakabayashi, 2004; Cynober, 2004; Evans et al., 2004; Tsuei et al., 2005). ORN was not infused, and increases in its levels are likely explained by the metabolic correlations existing between ORN availability and the availability of ARG, glutamate,

and other AA which may expand the glutamate pool (Wakabayashi, 2004; Cynober, 2004; Wu and Morris, 2004). Particularly interesting were the highly significant direct relationships found between increases in levels of ORN and increases in platelet and WBC counts, in cholesterol, fibrinogen and transferrin levels, and in plasma AA clearances. This was in turn associated with simultaneously increased AA infusion rates, and seemed to reflect a higher flow of substrate supporting ornithine, acute phase and other protein syntheses. The direct relationship with cholesterol ($r^2 = 0.4$, $p < 0.001$) was in agreement with previous observations that acute-phase hypocholesterolemia is moderated in the presence of increased AA substrate availability and increased plasma protein levels (Chiarla et al., 1989; Chiarla et al., 2004; Giovannini et al., 1999; Giovannini et al., in press). However, in spite of these highly significant findings, and although the existence of a supportive role of ornithine in synthetic processes is not a new concept (Oratz et al., 1983), the use of increasing plasma ORN as an index of adequacy of AA substrate availability must be confirmed by additional studies. This may be a main issue, given also the important link existing between availability of ORN and adequacy of function of immune cells (Mühling et al., 2004).

The relationship between ARG and the three branched chain amino acids (BCAA) LEU, VAL and ILE was also particularly interesting. Indeed, it was consistent with the tendency for increased metabolic use of ARG in simple trauma compared to sepsis, and with increased use of LEU, ILE and VAL in sepsis compared to trauma. Furthermore, although this is not pertinent to ARG metabolism, there was a tendency for a constant balance between the three BCAA levels (VAL:LEU:ILE $\approx$ 3.0:1.5:1.0). This finding was partly consistent with the results of basic investigations (Staten et al., 1984) and was reconfirmed in another group of similar patients infused with an enriched BCAA solution (not included in this study).

Another AA with an interesting link with ARG was LYS, which was directly and linearly related to it, and represented its best single correlate ($r^2 = 0.81$, $p < 0.001$). The relationship between plasma ARG and LYS was moderately though significantly affected by the AAIR, and the partial inversion of the ARG:LYS ratio which was present in the infused AA solution suggested an increased extravascular flux of ARG compared to LYS. The interdependency between ARG and LYS should be evaluated by taking into account that these AA share and compete for the same transport system (Devés and Boyd, 1998, Grillo and Colombatto, 2004b; Jozwik et al., 2004; Iapichino et al., 2004). This antagonism might become relevant in specific conditions (and perhaps also for ARG metabolism in sepsis) as it has been shown recently that the production of nitric oxide in experimental preparations may be reduced by increasing LYS availability, and thus probably by the competitive inhibition of ARG uptake by LYS (Stathopulos et al., 2001; Carter et al., 2004).

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