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Taurine and pulmonary hemodynamics in sepsis*

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Summary. This study has been performed to characterize the relationship between changes in plasma taurine (TAU) and hemodynamic patterns in sepsis. Analysis of 249 plasma aminoacidograms (AA-grams) and associated measurements in a group of critically ill, mechanically ventilated septic patients, showed that decreases in TAU were significantly correlated with increases in pulmonary artery pressure and pulmonary vascular resistance, and with worsening of pulmonary dysfunction. All cases requiring positive end-expiratory pressure greater than 10 cmH_2O had TAU lower than 50 μM/L. Low TAU was paralleled by decreases in other sulfur-containing AA, phosphoethanolamine, β-alanine, glutamate and aspartate, within a pattern of greater metabolic dysregulation. These data provide evidence of a link between severity of pulmonary dysfunction and reduced TAU availability in clinical sepsis. The implications relate also to the need for specific investigations of the clinical effect of exogenous TAU on proinflammatory mediator-induced pulmonary dysfunction.

Keywords: Amino acids – Taurine – Sepsis – Pulmonary hemodynamics – Respiratory failure – Phosphoethanolamine

Introduction

Taurine (TAU) is the most abundant free amino acid (AA). It influences cell function in the cardiovascular system and in other systems by a series of mechanisms, including regulation of cell osmotic and calcium homeostasis, membrane composition and stabilization and antioxidant defense; as a consequence, changes in TAU disposal have been associated with changes in cardiac inotropy, vascular tone, immune competence and anti-inflammatory

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protection (Wright et al., 1986; Huxtable, 1992; Chapman et al., 1993; Belli, 1994; Schaffer et al., 1995; Redmond et al., 1998; Stapleton et al., 1998). Although these properties of TAU and the reduction in plasma TAU found in sepsis have suggested a link between TAU deficiency and abnormal hemodynamics, the real relationship existing between TAU levels and hemodynamic patterns has never been assessed specifically (Askanazi et al., 1980; Vente et al., 1989; Jeevanandam et al., 1990; Paauw et al., 1990). This study has been carried on to perform such an assessment over a large group of measurements in a series of patients with post-traumatic sepsis.

Material and methods

Two hundred forty-nine determinations of plasma TAU were obtained together with full amino-acidograms and hemodynamic measurements in 16 (11 male, 5 female) patients with post-traumatic sepsis. Age was 30 ± 15 years (mean ± SD), mean body weight was 74.3 ± 14.5 Kg, height 176 ± 7 cm, body surface area 1.90 ± 0.20 m^2 (Du Bois and Du Bois, 1916), body mass index 23.9 ± 3.8 Kg/m^2. Medians of injury severity score (Greenspan et al., 1985) and sepsis severity score (Stevens, 1983; Skau et al., 1985) were 30 (range 11–54) and 29 (range 9–54), respectively. Three patients died. All patients were on mechanical ventilation with different levels of positive end-expiratory pressure (PEEP, cmH_2O). Sepsis was diagnosed on the basis of a temperature greater than 101.0°F (38.3°C), white blood cell count greater than 12,000 or less than 3,000 cell/mm^3, demonstration of a source of infection by a positive wound, abscess, or blood culture, or by a positive sputum culture in the case of respiratory infections (Chiarla et al., 1988). No patient had oliguric renal failure. Plasma samples for TAU and other AA determinations were obtained daily and analyzed in a Beckman AA analyzer. The plasma levels of AA, as determined from the blood samples, were then used to compute the mean clearance of each individual amino acid as described by Pittiruti et al. (1989). Simultaneous measurements included the determination of plasma lactate (mg/100 ml), cardiac index (CI, L/min/m^2) by the thermodilution method, mean blood pressure (MBP, mmHg), right atrial pressure (RAP, mmHg), pulmonary artery and wedge pressure (PAP, PWP, mmHg) and respiratory index (RI, units). Systemic and pulmonary vascular resistance (SVRI and PVRI, dyne·sec·cm^{-5}·m^2) were obtained from CI and pressure measurements. The patients were receiving total parenteral nutrition with glucose (270 ± 70 mg/Kg/h), fat (40 ± 35 mg/Kg/h) and AA (59 ± 22 mg/Kg/h) without exogenous TAU administration. Statistical analysis and validation of the results were performed by least-square regression analysis, with control of skewness and kurtosis, analysis of residuals and determination of 95% confidence intervals by the Scheffé criteria; control of variability was quantified by the r^2 value (coefficient of determination), the null hypothesis was tested by significance (p value) of the F ratio (Seber, 1977). A "best-fit" computer program was used to select, for each correlation, the regression yielding the best control of variability, based on Mallows' Cp criteria (Seber, 1977).

Results

Mean ± SD for plasma TAU and other AA levels and cardiopulmonary variables are reported in Table 1. Regression analysis on cardiopulmonary variables evidenced significant inverse correlations between PAP and TAU ($r^2 = 0.28$, $p < 0.001$), and between PVRI and TAU ($r^2 = 0.19$, $p < 0.001$) (Table 2, Fig. 1), while MBP and SVRI were unrelated to TAU. The inverse relationship found between PAP and TAU was reconfirmed in examining

Table 1. Plasma AA, metabolic and cardiorespiratory variables (mean ± SD)

ABU (μM/L)	21 ± 26
ALA (μM/L)	351 ± 233
ARG (μM/L)	102 ± 47
ASN (μM/L)	79 ± 85
ASP (μM/L)	8 ± 6
β-ALA (μM/L)	9 ± 11
CIT (μM/L)	17 ± 17
CYS (μM/L)	54 ± 23
CYSTA (μM/L)	11 ± 16
GLN (μM/L)	612 ± 452
GLU (μM/L)	68 ± 60
GLY (μM/L)	337 ± 210
HIS (μM/L)	124 ± 165
HYP (μM/L)	18 ± 14
ILE (μM/L)	81 ± 35
LEU (μM/L)	143 ± 56
LYS (μM/L)	194 ± 90
MET (μM/L)	72 ± 80
ORN (μM/L)	96 ± 63
PEA (μM/L)	10 ± 7
PHE (μM/L)	136 ± 77
PRO (μM/L)	298 ± 288
PSER (μM/L)	15 ± 7
SER (μM/L)	110 ± 64
TAU (μM/L)	88 ± 68
THR (μM/L)	144 ± 110
TRP (μM/L)	59 ± 13
TYR (μM/L)	71 ± 40
VAL (μM/L)	290 ± 122
Lactate (mg/100 ml)	16.25 ± 9.25
CI (L/min/m^2)	5.9 ± 1.8
MBP (mmHg)	90 ± 15
RAP (mmHg)	15 ± 5
PAP (mmHg)	29 ± 8
PWP (mmHg)	18 ± 5
SVRI (dyne·sec·cm^{-5}·m^2)	1,332 ± 440
PVRI (dyne·sec·cm^{-5}·m^2)	174 ± 92
RI (units)	1.6 ± 0.9

Table 2. Correlations between taurine and cardiopulmonary variables (n = 249)

PAP = -4.884 ($\log_e$ TAU) + 49.191	$r^2 = 0.28$
PWP = -2.578 ($\log_e$ TAU) + 28.519	$r^2 = 0.15$
PAP-PWP = -2.499 ($\log_e$ TAU) + 21.598	$r^2 = 0.21$
PVRI = -54.48 ($\log_e$ TAU) + 401.97	$r^2 = 0.19$
CI = $3.196 \cdot \text{TAU}^{0.136}$	$r^2 = 0.12$
RI = $3.920 \cdot \text{TAU}^{-0.261}$	$r^2 = 0.14$
PAP = 1.057 (PEEP) − 0.030 (TAU) + 24.039	$r^2 = 0.48$

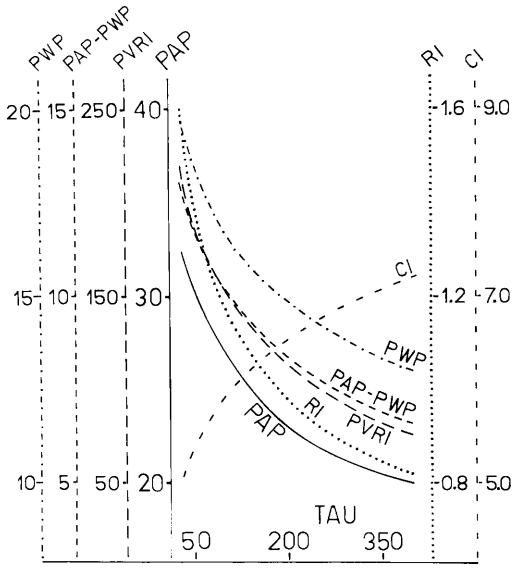

Fig. 1. Graphical display of equations in Table 2. Decreases in TAU are associated with a trend for increasing PAP, PVRI, PAP-PWP gradient, PWP and RI, and for decreasing CI (symbols and units as in the text; ranges and scales are set to ease simultaneous display of equations)

evolution of these variables in individual patient measurements. Weaker direct relationships were found between PAP or PVRI and alanine (ALA), phenylalanine (PHE) and tyrosine (TYR) ($r^2 = 0.18$ to 0.12, $p < 0.01$ for all), and between CI and TAU ($r^2 = 0.12$, $p < 0.01$), with an inverse relationship between lactate and TAU ($r^2 = 0.20$, $p < 0.001$). PAP and PVRI were unrelated to all other AA and AA clearances, with the exception of TAU clearance ($r^2 = 0.33$, $p < 0.001$); since TAU was not administered, this reflected only changes in plasma levels. Increasing PAP or PVRI, and decreasing TAU levels, tended to be correlated simultaneously with increasing RI ($r^2 = 0.21$ to 0.12, $p < 0.01$ for all) and worsening of respiratory dysfunction. In individual patients and in subgroups of measurements, the relationship between PAP and TAU was stronger than in the general population (with r^2 also greater than 0.45), due to suppression of inter-patient variability from concomitant factors. For instance, this was observed by separating cases ventilated with high levels of PEEP, and cases in cardiac failure, from the remainder: indeed, good relationships between PAP and TAU were maintained in the upper part of the PAP range by the former, and in the lower part by the latter, thus causing a spread in the general distribution when pooling cases together. To account for this effect, regression analysis was performed by considering PEEP as a simultaneous correlate of PAP, together with TAU, thus showing an independent contribution of TAU and PEEP to the variability of PAP. Both together accounted for 48% of this variability (multiple $r^2 = 0.48$, $p < 0.001$, Table 2). In all cases requiring PEEP greater than 10 cmH_2O, TAU level remained unexceptionally below 50 μM/L. Plasma AA-grams in these cases showed that most AA levels tended to

increase (leucine, valine, phenylalanine, tyrosine, alanine, proline, asparagine, threonine), or to remain constant (isoleucine, serine, glycine, glutamine, histidine, ornithine, arginine, lysine, citrulline), contrary to the decrease found for TAU (24 ± 10 vs 89 ± 70) and TAU analogues such as phosphoethanolamine (PEA) and β-alanine (β-ALA), and other sulfur-containing AA such as methionine and cystine or cysteine. Among these, more remarkable was the decrease in PEA, an AA whose changes correlated well with those of TAU ($r^2 = 0.70$, $p < 0.001$) and reached also its lowest levels in the sub-group of patients with PEEP $> 10\,cmH_2O$ (4 ± 2 vs 10 ± 7 μM/L). Decreases in the listed AA were paralleled also by lower glutamate and aspartate levels ($p < 0.001$). Regression analysis showed further that another important direct correlate of PAP was PWP. This was consistent with the observations performed in cases with cardiac failure. Inclusion of PWP as a simultaneous correlate of PAP, together with TAU and PEEP, brought the totally explained variability of PAP to 80% (multiple $r^2 = 0.80$, $p < 0.001$). Although this is important to report, the value of any quantifications is limited by measurement coupling between PWP and PAP, and by the circumstance that PWP becomes a less meaningful measurement during mechanical ventilation. Our analysis showed that also grouping of measurements according to plasma lactate levels yielded subgroups with an increased r^2 in regressions between PAP and TAU. However inclusion of lactate in multiple regressions did not add to the variability explained by PEEP and PWP, probably because severity of cardiorespiratory and metabolic decompensation, as quantified by lactate, was accounted for already by levels of PEEP and PWP.

Discussion

This study provides evidence of a relationship binding together PAP or PVRI and plasma TAU levels in sepsis. The finding was supported by an $r^2 = 0.28$, which is not high, nevertheless it reflected control of 28% of the variability of PAP and TAU. This was remarkable, given the multiple causes of variability affecting either PAP or TAU levels in sepsis. In particular, strength of this relationship was comparable to that found for more obvious determinants of PAP, such as PEEP and PWP, which accounted for large part of the residual variability of PAP (multiple $r^2 = 0.80$). Besides, the link found between PAP and TAU was rather unique, being unparalleled by similar relationships with other AA, and was reconfirmed by examining PAP and TAU evolution in individual patient measurements, where it accounted for an even larger percent of the variability of PAP ($r^2 > 0.45$). TAU is the most abundant free AA in the body, and is widely active in a series of processes, including regulation of osmotic and cellular calcium homeostasis, membrane composition and stabilization, antioxidant protection and detoxification; by these mechanisms TAU influences central nervous system and retinal development and function, cardiac inotropy and excitability, vascular tone, platelet aggregation, bile acid and xenobiotic conjugation and detoxification, and adequacy of immune response and protection from host tissue damage during

inflammation (Wright et al., 1986; Kendler, 1989; Guertin et al., 1991, 1993; Banks et al., 1992; Gordon et al., 1992; Huxtable, 1992; Pathirana and Grimble, 1992; Chapman et al., 1993; Belli, 1994; Cantin, 1994; Grimble, 1994; Schuller-Levis et al., 1994; Watson et al., 1995; Schaffer et al., 1995; Redmond et al., 1996, 1998; Neary et al., 1997; Stapleton et al., 1998; Malmezat et al., 1998). It is known that increased TAU disposal is associated with improved cardiac inotropy, and the findings in our study might be related to an effect of TAU on PAP mediated through changes in pulmonary blood flow. Although this would be consistent with the relationships found between CI or PWP and TAU (Table 2, Fig. 1) these were not sufficiently strong ($r^2 = 0.12$ and 0.15, respectively) to support such a possibility. Our findings could be related to a pathophysiologic coupling between PAP and TAU levels, with increasing PAP and decreasing TAU being determined simultaneously by worsening of the septic state. This may also be suggested by the simultaneous tendency for increased lactate, ALA, PHE and TYR levels (Cerra et al., 1979a,b, 1980; Siegel et al., 1979) and by previous empirical observations suggesting hypotaurinemia as a marker of more severe metabolic dysregulation in sepsis (unpublished observations). At the same time, however, a more direct link between PAP and TAU may be implicated. This could be related to the vasoactive properties of TAU (which has also been used clinically as an antihypertensive agent) (Kohashi et al., 1983; Kendler, 1989) or to a protective role of TAU against the inflammatory processes which contribute to raising PAP and PVRI in sepsis. Recently, great interest has been elicited by the evidence that requirement for TAU increases in sepsis for antioxidant and antiinflammatory protection (and for maintenance of immune competence) (Grimble, 1993, 1994; Redmond et al., 1996). It has been found experimentally that early increases in plasma TAU are elicited by the proinflammatory mediators of sepsis, are predictive of a more severe inflammatory response at pulmonary level, and that potentiation of TAU availability by exogenous support is protective against mediator-induced lung dysfunction (Banks et al., 1992; Gordon et al., 1992; Pathirana and Grimble, 1992; Park et al., 1993; Cantin, 1994; Schuller-Levis et al., 1994; Hofford et al., 1996; Hashiguchi et al., 1997). These findings are consistent with our observation that decreasing plasma TAU was associated with worsening of pulmonary dysfunction and increasing requirement for respiratory support. In cases requiring PEEP $>$ 10 cm H_2O, the fall in TAU was outstanding, with values never higher than 50 μM/L. The associated changes in other AA levels, besides showing a pattern generally indicative of more severe metabolic dysregulation (Cerra et al., 1979a,b, 1980; Siegel et al., 1979), were characterized by a reduction in sulfur-containing AA methionine and cystine or cysteine, and in glutamate and aspartate. This may reflect reduced substrate availability for gluthatione synthesis, and is also consistent with the impairment in antioxidant defense suggested already by TAU deficiency (Grimble, 1993, 1994). Decreases in TAU were also paralleled by simultaneous decreases in PEA and β-ALA. These may be related to metabolic, structural and receptor-binding analogies with TAU (Wu, 1976; Shotwell et al., 1983; Stipanuk, 1986; Grimble, 1993, 1994; Schaffer et al., 1995; Malmezat et al., 1998), however, the decrease in

PEA is also consistent with abnormally high PEA and phospholipid consumption for surfactant and cell replacement in ARDS lung (Gregory et al., 1991).

More study is needed not only to improve understanding of pathophysiology, but also to assess clinical implications, which cannot be established by our study. For instance, it may be relevant to confirm existence of a cause-effect relationship between inadequate TAU availability and severity of pulmonary changes, since TAU administration has been found already to protect against proinflammatory mediator-induced lung and liver dysfunction in experimental settings (Banks et al., 1992; Gordon et al., 1992; Pathirana and Grimble, 1992; Guertin et al., 1993; Cantin, 1994; Grimble, 1994; Schuller-Levis et al., 1994; Redmond et al., 1996; Stapleton et al., 1998).

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