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Co-variation of plasma sodium, taurine and other amino acid levels in critical illness*

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Summary. This study investigates the relationship between changes in plasma sodium and changes in amino acid levels in a patient with post-traumatic sepsis and prolonged critical illness. Ninety-two consecutive measurements were performed at regular intervals over a period of many weeks; these consisted in the determination of full amino-acidograms, plasma sodium and complementary variables. A unique, highly significant inverse correlation between taurine and plasma sodium was found ($r^2 = 0.48$, $p < 0.001$). All other amino acids were unrelated, or much more weakly related, to sodium. Taurine was also strongly and directly related to phosphoethanolamine, glutamate and aspartate. Changes in sodium and in levels of these amino acids explained up to 86% of the variability of taurine. Besides, levels of these amino acids maintained a high degree of co-variation, remaining reciprocally related one to each other, directly, with r^2 ranging between 0.33 and 0.59 ($p < 0.001$ for all). There were similar findings for β-alanine, which however was measured inconsistently. These data provide gross clinical evidence of a specific link binding plasma sodium and taurine levels, and may be consistent with occurrence of opposite and interdependent shifts of sodium and taurine between intravascular and extravascular space, to maintain osmoregulation. Co-variation of taurine with the other amino acids may be related to the same phenomenon, and/or to similarities in transport systems and chemical structure, or true metabolic interactions.

Keywords: Amino acids – Osmoregulation – Sepsis – Acute-phase response – Taurine – Phosphoethanolamine

Introduction

In critical illness and sepsis, changes in amino acid (AA) plasma levels have been linked to protein hypercatabolism, cytokine-mediated changes in intracellular AA transport systems, hepatic dysfunction and dysregulation of individual AA metabolism (Siegel et al., 1979; Cerra et al., 1980; Pittiruti et al., 1985; Hasselgren et al., 1986, Chiarla et al., 1997). Little is known about the relationship with changes in other plasma components, in particular those involved in fluid-electrolyte and osmotic balance. The issue has received considerable interest in experimental settings, while adequate "in vivo" characterization in human critical illness is still lacking. Also, recognition of these effects in large clinical samples is limited by inter-patient variability. We have investigated in a large number of measurements performed along the clinical course of a critically ill patient the relationship between plasma sodium (Na^+, the major extracellular ion involved in fluid-electrolyte and osmotic balance) and plasma AA, thus providing evidence of a significant inverse correlation binding taurine (TAU) to Na^+ levels (accounting for 48% of their variability), and of simultaneous co-variation of TAU with phosphoethanolamine (PEA), aspartate (ASP) and glutamate (GLU) levels.

Methods

Consecutive measurements were collected in a patient with post-traumatic sepsis and prolonged illness: after surgical repair of liver injury, he developed abdominal sepsis, then prolonged ventilatory insufficiency and finally a mild form of multiple organ dysfunction syndrome, before recovering. Measurements consisted in the determination of full amino-acidograms, plasma Na^+ (mEq/L), chloride (Cl^-, mEq/L) and complementary variables. These were performed twice every day, for a total of 92 measurements; β-alanine (β-ALA) was measured inconstantly and excluded from main results. Informed consent was obtained. The patient was undergoing total

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parenteral nutrition with glucose (6.3 ± 2.0 g/Kg/day, mean ± SD), amino acids (1.1 ± 0.4 g/Kg/day) and discontinuous fat (1.4 ± 0.8 g/Kg/day). Analysis of data was based on regression analysis by the least square technique, with skewness and kurtosis control, analysis of residuals and confidence limits, with a "simplest best fit" procedure allowing to select the simplest possible regressions yielding the largest control of variability of independent variables, based on Mallows' Cp criteria.

Results

Regression analysis, performed extensively over the whole sample of measurements, showed a highly significant inverse correlation between plasma TAU and Na^+ concentration ($r^2 = 0.48$, $p < 0.001$); all other AA were directly correlated or not correlated to Na^+, with the partial exception of PEA, GLU and ASP, which maintained with Na^+ weak inverse correlations of borderline significance.

The relationship between TAU and the other AA levels was then explored. While most AA levels were inversely and weakly correlated or not correlated to TAU, there were relatively strong correlations between PEA, GLU, ASP and TAU ($r^2 = 0.59$, 0.41 and 0.39, respectively, $p < 0.001$ for all). The r^2 for ASP was decreased by tendency for a looser correlation at low TAU levels (TAU < 40 μM/L). The simultaneous relationships between TAU, Na^+ and levels of each one of these AA are quantified in regressions in which changes in Na^+ and in levels of these AA explained from 70% to 86% of the variability of TAU (multiple r^2 from 0.70 to 0.86, Table 1 and Fig. 1). Besides, PEA, GLU and ASP maintained a high degree of co-variation, remaining reciprocally related one to each other, directly, with r^2s ranging between 0.33 and 0.59 ($p < 0.001$ for all). Neither TAU nor these AA were infused with the parenteral nutrition. It is worth mentioning that also β-ALA, measured inconstantly, was related directly to TAU ($p < 0.01$), and maintained patterns of correlation with the other AA similar to those of TAU.

As expectable, Cl^- concentration was directly and strongly related to Na^+ ($r^2 = 0.71$, $p < 0.001$), and maintained with other variables relationships similar to those found for Na^+, although with lower r^2s; Cl^- was also related inversely to TAU ($r^2 = 0.27$, $p < 0.001$), but lost significance as a correlate of TAU when considered together with Na^+ in the same regression.

Finally, it is worth mentioning that the inverse relationship found between TAU and Na^+ ($r^2 = 0.48$) was not influenced along the clinical course by changing patterns of illness (apart from tendency for lower TAU levels in stages with more severe respiratory and metabolic decompensation). Besides, r^2 of the same relationship rose from 0.48 to 0.68 when Na^+ was converted into the corresponding estimate of plasma osmolality (Goldberger, 1975). Also, it was not influenced by the discontinuous infusion of fat, and by changes in doses of other parenteral substrates and in urine output.

Table 1. Simultaneous relationships between plasma taurine (TAU, μM/L), sodium (Na^+, mEq/L) and levels of phosphoethanolamine (PEA, μM/L), aspartate (ASP, μM/L) and glutamate (GLU, μM/L)

TAU = 707.1 + 7.3(PEA) − 4.6(Na^+)	$r^2 = 0.86$, $p < 0.001$*
TAU = 968.5 + 10.5(ASP) − 6.5(Na^+)	$r^2 = 0.72$, $p < 0.001$
TAU = 756.4 + 1.0(GLU) − 4.8(Na^+)	$r^2 = 0.70$, $p < 0.001$

Mean ± SD values (and ranges): Na^+ = 145 ± 8 mEq/L (132–159), TAU = 95 ± 69 μM/L (18–280), PEA = 8 ± 6 μM/L (1–32), ASP = 7 ± 3 μM/L (1–18), GLU = 39 ± 34 μM/L (6–173).
* Graphical display in Fig. 1

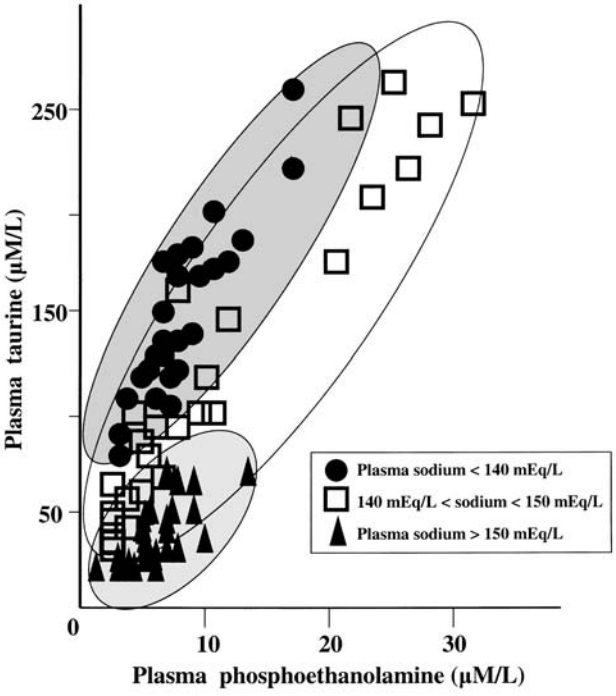

Fig. 1. Changes in plasma taurine are related simultaneously to directionally similar changes in phosphoethanolamine and to opposite changes in sodium (measurement points labeled and encircled according to sodium levels). Similar displays are obtainable by substituting aspartate or glutamate for phosphoethanolamine. Exact quantification of these relationships in Table 1

Discussion

Our results demonstrate, as a unique feature of TAU, a strong inverse correlation with Na^+, accounting for 48% of its variability ($r^2 = 0.48$), and a simultaneous link between changes in TAU and changes in levels of PEA, ASP and GLU (and β-ALA). While some degree of direct correlation among different AA, and among Na^+ and AA concentrations, could be predictable (for instance, as a consequence of hemodilution or hemoconcentration) the strong inverse correlation found between TAU and Na^+ is an important exception, suggesting that a specific link is binding these two variables. Our findings in this patient are consistent with occurrence of opposite and interdependent shifts of TAU and Na^+ between intravascular and extravascular space, and probably with clinical evidence of a contribution of TAU to osmoregulation (although our study does not assess other possibly contributing factors, such as TAU and Na^+ interactions at renal level) (Hayes et al., 1988; Kohashi et al., 1989; Chesney et al., 1990; McBroom et al., 1998; Ciechanowska, 1997). This effect has been described extensively over the years, in a large body of experimental studies (Thurston et al., 1980; Kregenov, 1981; Hoffman et al., 1992; Atlas et al., 1984; Solis et al., 1988; Trachtman et al., 1988, 1990, 1995; Lien et al., 1990; Huxtable, 1992; Burg, 1995; Stummer et al., 1995; Law, 1998; Guizouarn et al., 2000; Schaffer et al., 2000; De Luca et al., 2001); it involves co-transport of Cl^- together with TAU and Na^+, and has not yet been assessed fully in its complexity. TAU is one of the more important organic osmolytes, whose advantage is the possibility to contribute to osmoregulation without interfering excessively with physico-chemical patterns and Gibbs-Donnan equilibrium at cellular level. In particular, the protective effect of TAU on the brain in response to osmotic stress is a well-known feature, and may involve also protection from central pontine myelinolysis during correction of hyponatremia (Lien et al., 1991, 1995). Osmoregulation as the underlying mechanism for the inverse relationship found between Na^+ and TAU is also consistent with the co-variation of levels of TAU with PEA, ASP, and GLU (and β-ALA). Co-variation of these AA in extracellular fluid has been observed already in many experimental settings. These AA have very high intracellular concentrations, and co-variation in their plasma levels may be related to shifts in intracellular/extracellular AA pools to maintain osmotic balance (a role which seems to be common to all of them, although more relevant for TAU), to similarities in intracellular AA transport systems, analogies in chemical structure and membrane receptor binding, interactions in neurotransmission and co-release from cells (Griffith, 1983, 1986; Shotwell et al., 1983; Lehmann et al., 1985, 1990; Milakofsky et al., 1985, 1989; Solis et al., 1988; Trachtman et al., 1988; Lien et al., 1991, 1995; Becquet et al., 1993; Hamberger et al., 1993; Klunk et al., 1995; Schaffer et al., 1995; Hofford et al., 1996; Song et al., 1998; Phillis et al., 1999). Also true metabolic relationships may be involved, based on the metabolic balance existing between GLU and ASP, and on the notion that GLU may be a substrate for TAU synthesis (through cysteinesulfinate) (Stipanuk, 1986; Hayes, 1988; Skeie et al. 1990).

For completeness it is worth mentioning that the best fit between TAU and Na^+ in our patient was a nonlinear one. However, deviation from linearity was related to changes in PEA, ASP or GLU, so that use of nonlinear functions was not necessary any more when those variables were included in the regression together with TAU and Na^+ (such as in Table 1). Also, the looser correlation found between TAU and ASP for TAU $< 40\,\mu$M/L was related to abnormal changes in Na^+ ($Na^+ > 150$ mEq/L), so that the cut-off at TAU $< 40\,\mu$M/L was not necessary any more when TAU, ASP and Na^+ were considered together in the same regression (such as in Table 1). These observations provide additional evidence of interdependency of changes in TAU, Na^+, PEA, ASP and GLU levels. Furthermore, a pattern similar to that described in this patient (that is, evidence of an inverse correlation between TAU and Na^+ on graphical display) was observed in 13 additional patients with trauma and sepsis in whom these measurements were available. In all of them, however, number of measurements, length and complexity of illness and ranges of variation of TAU and Na^+ were smaller than in the case described in the manuscript, so that statistical significance was reached in only 6 cases (in 3 with r^2s between 0.40 and 0.69, $p < 0.05$ for all). When pooling all available measurements from all patients together, the same relationship was reconfirmed, however with a lower r^2 ($r^2 = 0.15$, $p < 0.001$, $n = 353$). This was due to differences in the ranges of TAU and Na^+ in different patients, causing dispersion of observations in the general distribution. Again, inclusion of PEA, ASP or GLU in the regression together with TAU and Na^+ increased largely the r^2, thus suggesting that the observed inter-patient

variability was related to differences in levels of these AA, and reconfirming once more their link with TAU and Na^+ levels.

In spite of all these findings, caution must still be used in relating results of specific experiments on TAU and osmoregulation, performed mostly "in vitro" and in animal tissues, to our findings on human plasma. Besides, there is specificity of TAU release and uptake in different tissues, and it may be an oversimplification to consider changes in plasma levels of TAU as reflecting a general balance for whole body districts. Nevertheless, the highly significant relationship found between TAU and Na^+ in our critically ill patient suggests that this is a more general phenomenon, well quantifiable also in human illness.

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References

Atlas M, Bahl JJ, Roeske WW, Bressler R (1984) In vivo osmoregulation of taurine in fetal mouse heart. J Mol Cell Cardiol 16: 311–320

Becquet D, Hery M, Francois-Bellan AM, Giraud P, Deprez P, Faudon M, et al (1993) Glutamate, GABA, glycine and taurine modulate serotonin synthesis and release in rostral and caudal rhomboencephalic raphe cells in primary cultures. Neurochem Int 23: 269–283

Burg MB (1995) Molecular basis of osmotic regulation. Am J Physiol 268: F983–F996

Cerra FB, Siegel JH, Coleman B, Border JR, McMenamy RR (1980) Septic autocannibalism. A failure of exogenous nutritional support. Ann Surg 192: 570–580

Chesney RW, Zelikovic I, Jones DP, Budreau A, Jolly K (1990) The renal transport of taurine and the regulation of renal sodium-chloride-dependent transporter activity. Pediatr Nephrol 4: 399–407

Chiarla C, Giovannini I, Siegel JH, Boldrini G, Castagneto M (1997) Proline metabolism in sepsis. Amino Acids 12: 237–247

Ciechanowska B (1997) Taurine as a regulator of fluid-electrolyte balance and arterial pressure. Ann Acad Med Stetin 43: 129–142

De Luca G, Calpona PR, Caponetti A, Romano G, Di Benedetto A, Cucinotta D, Di Giorgio RM (2001) Taurine and osmoregulation: platelet taurine content, uptake and release in type 2 diabetic patients. Metabolism 50: 60–64

Goldberger E (1975) A primer of water, electrolyte and acid-base syndromes. Syndromes associated with disturbed osmolality. 2nd edn. Lea and Febiger, Philadelphia, pp 138–148

Griffith OW (1983) Cysteinesulfinate metabolism. Altered partitioning between transamination and decarboxylation following administration of β-methyleneaspartate. J Biol Chem 258: 1591–1598

Griffith OW (1986) β-amino acids. Mammalian metabolism and utility as α-amino acid analogues. Annu Rev Biochem 55: 855–878

Guizouarn H, Motais R, Garcia-Romeu F, Borgese F (2000) Cell volume regulation: the role of taurine loss in maintaining membrane potential and cell pH. J Physiol 523: 147–154

Hamberger A, Haglid K, Nyström B, Silfvenius H (1993) Covariation of free amino acids in human epileptogenic cortex. Neurochem Res 18: 519–525

Hasselgren PO, James JH, Fischer JE (1986) Inhibited muscle amino acid uptake in sepsis. Ann Surg 203: 360–365

Hayes KC (1988) "Vitamin-like" molecules: taurine. In: Shils ME, Young VR (eds) Modern nutrition in health and disease, 7th edn. Lea and Febiger, Philadelphia, pp 464–470

Hoffman EK (1992) Cell swelling and volume regulation. Can J Physiol Pharmacol 70S: 310–313

Hofford JM, Milakofsky L, Pell S, Vogel W (1996) A profile of amino acid and catecholamine levels during endotoxin-induced acute lung injury in sheep: searching for potential markers of the acute respiratory distress syndrome. J Lab Clin Med 128: 545–551

Huxtable RJ (1992) Physiological actions of taurine. Physiol Rev 72: 101–163

Klunk WE, Mc Clure RJ, Xu C-J, Pettegrew JW (1995) Structural determinants of activity at the GABAB receptor. A comparison of phosphoethanolamine and related GABA analogues. Mol Chem Neuropathol 26: 15–30

Kohashi N, Okabayashi T, Horiuchi M, Nishiyama H, Takenaka T, Katori R (1989) Mechanism of taurine natriuresis in rats. Adv Exp Med Biol 247A: 635–640

Kregenov FM (1981) Osmoregulatory salt transporting mechanisms: control of cell volume in anisotonic media. Annu Rev Physiol 43: 493–505

Law RO (1998) The role of taurine in the regulation of brain cell volume in chronically hyponatremic rats. Neurochem Int 33: 467–472

Lehmann A (1990) Derangements in cerebral osmohomeostasis: a common denominator for stimulation of taurine and phosphoethanolamine release. Progr Clin Biol Res 351: 337–347

Lehmann A, Lazarewicz JW, Zeise M (1985) N-methylaspartate-evoked liberation of taurine and phosphoethanolamine in vivo: site of release. J Neurochem 45: 1172–1177

Lien YH (1995) Role of organic osmolytes in myelinolysis. A topographic study in rats after rapid correction of hyponatremia. J Clin Invest 95: 1579–1586

Lien YH, Shapiro JI, Chan L (1990) Effects of hypernatremia on organic brain osmoles. J Clin Invest 85: 1427–1435

Lien YH, Shapiro JI, Chan L (1991) Study of brain electrolytes and organic osmolytes during corrction of chronic hyponatremia. Implications for the pathogenesis of central pontine myelinolysis. J Clin Invest 88: 303–309

McBroom MJ, Qureshi A, Davidson N (1998) Antidiuretic hormone infusion reduces taurine and NaCl-induced hypernatremia in the rat. Amino Acids 15: 89–97

Milakofsky L, Hare TA, Miller JM, Vogel WH (1985) Rat plasma levels of amino acids and related compounds during stress. Life Sci 36: 753–761

Milakofsky L, Miller JM, Vogel WH (1989) Effect of ethanol on plasma amino acids and related compunds of stressed male rats. Pharmacol Biochem Behav 32: 1071–1074

Phillis JW, Song D, O'Regan MH (1999) Effects of hyperosmolarity and ion substitutions on amino acid efflux from the ischemic rat cerebral cortex. Brain Res 828: 1–11

Pittiruti M, Siegel JH, Sganga G, Coleman B, Wiles CE, Belzberg H, Wedel S, Placko R (1985) Increased dependence on leucine in post-traumatic sepsis: leucine/tyrosine clearance ratio as indicator of hepatic impairment in septic multiple organ failure. Surgery 98: 378–387

Schaffer SW, Azuma J, Madura JD (1995) Mechanisms underlying taurine-mediated alterations in membrane function. Amino Acids 8: 231–246

Schaffer S, Takahashi K, Azuma J (2000) Role of osmoregulation in the actions of taurine. Amino Acids 19: 527–546

Shotwell MA, Kilberg MS, Oxendel DL (1983) The regulation of neutral amino acid transport in mammalian cells. Biochim Biophys Acta 737: 267–284

Siegel JH, Cerra FB, Coleman B, Giovannini I, Shetye M, Border JR, McMenamy RR (1979) Physiological and metabolic correlations in human sepsis. Surgery 86: 163–193

Skeie B, Kvetan V, Gil KM, Rothkopf MM, Newsholme EA, Askanazi J (1990) Branch-chain amino acids: their metabolism and clinical utility. Crit Care Med 18: 549–571

Solis JM, Herranz AS, Herrears O, Lerma J, Martin del Rio R (1988) Does taurine act as an osmoregulatory substance in the rat brain? Neurosci Letters 91: 53–58

Song D, O'Regan MH, Phillis JW (1998) Amino acid release during volume regulation by cardiac cells: cellular mechanisms. Eur J Pharmacol 341: 273–280

Stipanuk MH (1986) Metabolism of sulfur-containing amino acids. Annu Rev Nutr 6: 179–209

Stummer W, Betz AL, Shakui P, Keep RF (1995) Blood-brain barrier taurine transport during osmotic stress and in focal cerebral ischemia. J Cereb Blood Flow Metab 15: 852–859

Thurston JH, Hauhart RE, Dirgo JA (1980) Taurine: a role in osmotic regulation of mammalian brain and possible clinical significance. Life Sci 26: 1561–1568

Trachtman H, Barbour R, Sturman JA, Finberg L (1988) Taurine and osmoregulation: taurine is a cerebral osmoprotective molecule in chronic hypernatremic dehydration. Pediatr Res 23: 35–39

Trachtman H, del Pizzo R, Sturman JA (1990) Taurine and osmoregulation. III. Taurine deficiency protects against cerebral edema during acute hyponatremia. Pediatr Res 27: 85–88

Trachtman H, Yancey PH, Gullans S (1995) Cerebral volume regulation during hypernatremia in developing rats. Brain Res 693: 155–162

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