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The plasma levels of CST and BCKDK in patients with sepsis

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ABSTRACT

Objectives: CST has been recently identified as a mediator of various beneficial effects in animal models of sepsis. At present, no data are available concerning the levels of CST in sepsis patients. In sepsis the plasma amino acid pattern is characterized by decreased branced chain amino acids (BCAAs). We investigated the levels of plasma CST or branched-chain α-ketoacid dehydrogenase kinase (BCKDK) and their relationship to component traits in patients with sepsis.
Design and methods: We studied 228 patients and divided them into two groups based on severity of infection. Blood samples were taken at study entry, and CST, BCKDK were measured.
Results: CST and BCKDK levels were significantly higher in patients with sepsis than in controls: the median plasma CST concentration was 103.1 ng/ml (range, <83.13–189.7 ng/ml) in patients with sepsis and 49.69 ng/ml (range, <19.38–100.8 ng/ml) in controls ($p = 0.0022$); the median plasma BCKDK concentration was 801.7 ng/ml in sepsis group and 745 ng/ml in controls ($p = 0.0292$). Additionally, there was correlation between the plasma concentrations of CST and BCKDK in sepsis patients ($r^2 = 0.6357$, $p < 0.01$).
Conclusions: We conclude that the plasma levels of CST in sepsis patients were higher than in controls, and there is a relationship between CST and BCKDK in sepsis patients. Future experimental and clinical studies are needed to evaluate CST as a novel prognostic tool in sepsis patients and its potential therapeutic use in sepsis.

1. Introduction

Severe sepsis and septic shock are among the leading causes of admission to intensive care units (ICUs), with high mortality rates [1,2]. Care for patients with sepsis represents a great economic burden [3]. Diagnosing sepsis is very difficult because its symptoms are vague and nonspecific. And antibiotics are administered before culture results are obtained to reduce morbidity and mortality rates-increasing antibiotic resistance and hospital charges.

Recently, the effectiveness of procalcionin (PCT) as an early diagnostic tool for sepsis has been reported. PCT is a peptide composed of 116 amino acid, prohormone, calcitonin precursor. Serum concentrations in healthy individuals are extremely low, <0.05 ng/ml, or even immeasurable [4]. High PCT concentrations are typically found in bacterial infection [5]. Under the influence of inflammatory cytokines and bacterial endotoxin, it is produced in a number of tissues, such as lung, liver, kidney and so on, and goes in circulation, when its level can increase up to 1000 times [6,7]. PCT is a stable marker, whose concentration is not affected by neutropenia, immunodeficiency conditions and the use of nonsteroid and ateroid anti-inflammatory drugs, which is not the case with CRP [8].

In sepsis the plasma branced chain amino acids (BCAA: valine, leucine, isoleucine) pattern is characterized by normal or decreased [9]. BCAA catabolism is irreversible oxidative decarboxylation of the branched-chain α–keto acids catalyzed by the mitochondrial branched-chain α–keto acid dehydrogenase(BCKD) complex. The activity of the complex within a tissue is regulated by phosphorylation and dephosphorylation catalyzed by a specific kinase(BCKDK) and phosphatase [10].

Cortistatin (CST) is a cyclic neuropeptide, which was discovered in 1996, with multiple biological activities, was named after

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its predominantly cortical expression and ability to depress cortical activity [11]. CST exerts various biological functions, such as protecting neurons against ischemic injury and cytotoxic damage [12], suppressing the proliferation of tumor cells [13], inhibiting inflammation and inducing immune tolerance [14] and endocrine secretions and metabolic functions, exogenous CST has been shown to inhibit pituitary GH and pancreatic insulin release [15,16]. Previous study indicated that CST protected against endotoxin-induced lethality and prevented the septic shock-associated histopathology, including inflammatory cell infiltration and multiorgan intravascular disseminated coagulation [17]. This therapeutic effect of CST was mediated by decreasing the local and systemic levels of a wide spectrum of inflammatory mediators, including cytokines, chemokines, and acute phase proteins [17]. Our previous study found CST could attenuate sepsis-induced cardiac dysfunction and myocardial apoptosis through inhibiting endoplasmic reticulum stress (ERS) and NLRP3 inflammasome [18,19].

However, the exact changes of endogenous CST in patients with sepsis, and the levels of CST whether associate with sepsis severity remain unknown. In addition, it is undetermined whether endogenous CST plays a major role participate in amino acid metabolism in patients with sepsis. In this study, we investigated plasma CST and branched-chain α-ketoacid dehydrogenase kinase (BCKDK) levels and their relation to component traits in patients with sepsis.

2. Materials and methods

2.1. Patients and sample collection

Data were collected during a 12-month period between January and December 2014, department of Emergency at The First Affiliated Hospital of Harbin Medical University. We included 228 patients in the study, they all body temperature above 38 °C or below 36 °C when they hospitalized. Then divided them into two groups based on the severity of infection [20,21]. (1) control group: no infection and PCT < 0.5 ng/ml; (2) sepsis group: confirmed sepsis group (>3 positive sepsis-related clinical symptoms; >2 positive sepsis-related blood test results; positive blood culture test results; and PCT>1 ng/ml). The study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Harbin Medical University and complied with the Declaration of Helsinki, and informed consent was obtained from subjects before the initiation of the study. Patients with the following diseases were excluded from the study: acute myocardial infarction; immune diseases.

Plasma was obtained by centrifugation at 1200*g* for 10 min at 4 °C and stored until the assay.

2.2. Methods

CST and BCKDK levels were measured by ELISA kits, which were obtained from the Shanghai Yanjin Bioengineering Company (Shanghai, China). The ELISAs was created as previously described [22], which employed specific capture antibodies coated on a 96-well plate. Standards and blood samples were pipette into the wells; the target protein in the standards and samples binds to the immobilized antibody. The wells were washed and the biotin-labeled detection antibody was then added. After washing away the unbound biotinylated antibodies, HRP-conjugated streptavidin was pipette to the wells, followed by a colorimetric substrate solution. The intensity of color development in the wells was proportional to the amount of target protein bound. The levels of PCT, lactic acid, platelet and serum creatinine were assessed by routine biochemical analysis.

Table 1
Clinical and biochemical characteristics of the study groups.

Variables	Control(n = 96)	Sepsis(n = 132)
Age (years)	42(38.75–47.25)	48(42–60)
Male/female	46/50	72/60
BMI (kg/m^2)	24.2 ± 2.7	24.7 ± 2.4
PCT (ng/ml)	0.18 ± 0.32	38.4 ± 51*
Lactic acid (mmol/L)	2.4 ± 2.7	3.0 ± 2.1*
Platelet (×10^9/L)	200 ± 125	209 ± 157
Serum creatinine (mg/dl)	1.8 ± 1.5	2.0 ± 1.5

BMI, Body Mass Index; PCT, procalcitonin.
* $p < 0.05$ vs. controls.

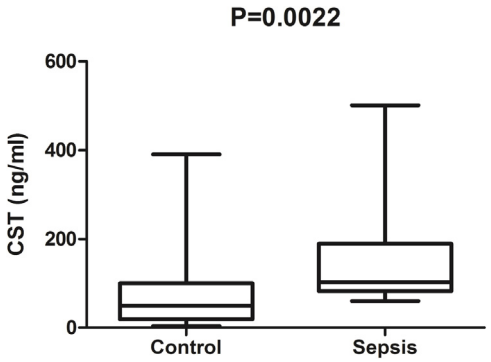

Fig. 1. CST levels in controls and patients with sepsis. Control group 49.69 ng/ml (range, <19.38–100.8 ng/ml, n = 96); sepsis group 103.1 ng/ml (range, <83.13–189.7 ng/ml, n = 132).

2.3. Statistical analysis

Data were reported as the means (standard deviations) or medians (interquartile range) for continuous variables and as numbers (percentages) for categorical variables. The differences between two groups were analyzed using Student's *t* test or the nonparametric Wilcoxon test for continuous variables and the X^2 test for categorical variables. One-way ANOVA was used to compare data of more than two groups. Associations between the plasma CST and BCKDK levels were evaluated using the Spesrman correlation test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Subject profiles

The characteristics of the subjects are given in Table 1. Patients with sepsis and controls did not differ in age and gender. Patients with sepsis showed significantly higher lactic acid than control group.

3.2. Plasma CST in patients with sepsis

Notably, the plasma CST levels were significantly higher in patients with sepsis than in controls: the median plasma CST concentration was 49.69 ng/ml (range, <19.38–100.8 ng/ml) in controls and 103.1 ng/ml (range,<83.13–189.7 ng/ml) in patients with sepsis (p = 0.0022) (Fig. 1). Compared with the PCT < 0.5 group, the level of CST in 0.5 < PCT < 2 group increased by 2.2-fold ($p < 0.05$). The level of CST in PCT > 2 group is higher than PCT < 0.5 group, but there is no statistical significance (Fig. 2). In order to observe the potential correlation between CST and PCT, we also showed each patient's CST and PCT levels(Fig. 3). Then we included 132 mild infection patients (>2 positive sepsis-related clinical symptoms; <2 positive sepsis-related blood test results; negative blood culture test results) in the study and divided them into 4 groups based on the only site