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TRANSLATIONAL STUDIES ON ADRENOCORTICAL FUNCTION IN HEALTH AND DISEASE

Steroid:Corticosteroid-Binding Globulin Interactions; Effects of Neutrophil Elastase Cleavage, Pyrexia and Acidosis.

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Context Corticosteroid-binding globulin (CBG) transports cortisol and other steroid hormones[1,2]. High-affinity CBG (haCBG) undergoes proteolysis of the reactive centre loop (RCL) by neutrophil elastase (NE) at inflammatory sites, liberating immunomodulatory cortisol and altering conformation to low-affinity CBG (laCBG). Pyrexia reduces CBG:cortisol binding affinity, an interaction at the RCL is speculated[3]. **Objective** To measure the equilibrium binding constants of a panel of steroids to glycosylated haCBG and laCBG over temperature and pH ranges mimicking the pathophysiological conditions of septic shock. **Design** Surface plasmon resonance was used to determine the binding profiles of 19 steroid ligands to haCBG and laCBG at temperatures 25°C, 37°C and 39°C and pH 7.4 and 7.0. The RCL-recognizing 9G12 antibody was used to assess cleavage and epitope availability of the RCL across conditions. **Results** A 4–8 fold reduction in affinity for cortisol, cortisone, corticosterone, 11-deoxycortisol, progesterone, 17-hydroxyprogesterone and prednisolone occurred with NE-mediated haCBG-to-laCBG conversion, cortisol expectedly displayed the highest binding affinity. Binding affinity consistently decreased at higher temperatures and at acidic pH for both haCBG and laCBG. 9G12 antibody RCL binding was preserved for haCBG across temperatures. **Conclusions** These studies reveal that steroid binding to CBG is selective and in all cases reduced upon NE-mediated haCBG-to-laCBG transition. Moreover, reduced CBG:cortisol binding affinity at elevated temperature occurs with an intact and accessible RCL epitope, suggesting a non-RCL mechanism for the delivery of anti-inflammatory cortisol in pyrexia. Synergy of NE cleavage and pyrexia/acidosis may serve for local inflammatory site cortisol delivery and increase free cortisol. These findings demonstrate the modifiable hormone binding characteristics of CBG in (patho-)physiological conditions, supporting its significance in cortisol delivery in obviating systemic inflammation and multiorgan-organ failure in patients with septic shock and its association with mortality[4].

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ADRENAL - HYPERTENSION

Validating and Optimizing the Guideline Criterion for Skipping Confirmatory Tests of Primary Aldosteronism

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Abstract

Background: Confirmatory tests of primary aldosteronism (PA), including saline infusion test (SIT), captopril challenge test (CCT) and fludrocortisone suppression test (FST), are recommended by the Endocrine Society Clinical Practice Guideline. In order to simplifying diagnostic process, a criterion for skipping confirmatory tests was established by the guideline, while the evidence is lacking.

Objective: To validate and optimize the guideline criterion for skipping confirmatory tests.

Design: Prospective diagnostic study.

Setting: Chongqing, China.

Measurements: A total of 501 patients with high risk of PA were retrospectively enrolled. All of them completed at least two confirmatory tests (CCT, SIT, and FST). The guideline criterion is: history of spontaneous hypokalemia, plasma renin concentration (PRC) below detection levels and plasma aldosterone (PAC)>20ng/dl (550pmol/L). An optimized criterion (history of spontaneous hypokalemia, PRC <2.5 uIU/ml and PAC>20 ng/dl) was established based on the guideline criterion. Parameters such as sensitivity, specificity and area under the receiver-operator characteristic curves (AUC) were calculated to compare the diagnostic value of these two criteria.

Results: Using SIT, CCT and FST (cutoffs: PAC post-SIT 10 $ng \cdot dl^{-1}$; PAC post-CCT 11 $ng \cdot dl^{-1}$; PAC post-FST 6 $ng \cdot dl^{-1}$) for PA diagnosis, the specificity of the guideline criterion was 1.00 (0.98–1.00), 1.00(0.98–1.00) and 1.00(0.97–1.00) respectively, while the sensitivity was 0.12 (0.09–0.17), 0.12(0.08–0.16) and 0.09(0.06–0.12) respectively. Compared to the guideline criterion, the sensitivity of the optimized criterion was significantly improved [SIT: 0.42 (0.36–0.49); CCT: 0.41 (0.35–0.48); FST: 0.30 (0.25–0.34), all the *P values* < 0.001 when compared to the guideline criterion]. However, the specificity of the optimized criterion was similar to the guideline criterion (all the *P values*>0.05).

Limitation: This study was carried out in a single center.

Conclusions: The guideline criterion shows high specificity but low sensitivity for direct diagnosis of PA. The