Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS

Angiotensin II Induces Aldosterone Synthesis in the Rat Heart Stressed by Angiotensin II

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Aldosterone (Aldo) causes myocardial injury and fibrosis. While most Aldo is made by the adrenal zona glomerulosa; there have been controversial reports that Aldo is also synthesized in the heart; such myocardial synthesis of Aldo might contribute to myocardial injury. We induced cardiac fibrosis in rats by infusing angiotensin II (AngII) @ 500 ng/kg/min via subcutaneous pumps. After 4 weeks, circulating corticosterone increased about 400-fold from ~29 nM to ~11 μM. Aldo synthesis in isolated mitochondria (mito) was assessed by conversion of tritiated deoxycorticosterone to Aldo; AngII infusion doubled Aldo synthesis, and this augmented synthesis was inhibited in mito from rats receiving AngII + telmisartan, which inhibits the binding of AngII to the AT1 receptor. Western blotting showed P450c11AS (Aldo synthase) was also stimulated by AngII and inhibited by telmisartan in both rat heart and H9c2 myocardial cells. 2-dimentional native PAGE and mass spectrometry showed that a 290-kDa complex on the inner mitochondrial membrane (IMM) contained P450c11AS, Tom22 (a translocase associated with the outer mitochondrial membrane, OMM), and StAR (the steroidogenic acute regulatory protein). Immunocytochemistry and transmission electron microscopy monitoring of immune-gold particles confirmed that P450c11AS, Tom22, and StAR were associated with the mito, that P450c11AS and StAR were associated with the IMM and that P450c11AS and StAR, but not Tom22, were increased by AngII. Cardiac Aldo synthesis required myocardial expression of P450c11AS, but expression of P450scc, the initial steroidogenic enzyme that converts cholesterol to pregnenolone, was undetectable, indicating the heart cannot make Aldo *de novo* from cholesterol. The only known action of StAR is to promote the movement of cholesterol from the OMM to IMM; nevertheless, we found that intramitochondrial StAR is required for Aldo synthesis; protein crosslinking with BS3 showed that Tom22 forms a bridge between StAR and P450c11AS. This is the first activity ascribed to intramitochondrial StAR, but the manner by which StAR promotes P450c11AS activity is unclear. As P450scc was undetectable, and circulating concentrations of corticosterone approached the Km (~28 μM) for the use of corticosterone as a substrate for P450c11AS, we suggest that cardiac P450c11AS uses circulating steroids for substrate. Thus the stressed heart produces aldosterone using a previously undescribed intramitochondrial mechanism that involves P450c11AS, Tom22 and StAR

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

High Mortality Rate in Oral Glucocorticoid Users: A Case-Control Study

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Objective. Long-term oral glucocorticoid (GC) use is associated with increased mortality in patients with rheumatoid arthritis and inflammatory bowel disease. The aim of the study was to investigate whether there is excess mortality among oral GC users, regardless of the underlying disease.
Methods. This was a retrospective case-control study. Information on dispensed prescriptions was obtained from the Swedish Prescribed Drug Register. Patients receiving ≥5 mg prednisolone (or equivalent dose of other GC) daily for ≥21 days between 2007-2014 were included. For each patient, a control person, matched for age and sex, was included. The cause of death was obtained from the Swedish Cause-of-Death Registry. Hazard ratio (HR) for mortality was calculated by using Cox proportional hazard model and by the log-rank test. The GC users were divided into four groups according to the length of GC treatment: 1) single-occasion users 2) occasional users (<300 tablets/year); 3) medium-term users (> 300 tablets/year for ≤ 2 consecutive years); and 4) long-term users (>300 tablets/year for > 2 consecutive years).
Results. Of 1,585,335 inhabitants in Western Sweden, 223,211 GC users (women 55.6%) were identified for the analysis. The mean age was 48 ± 24 years. Median follow-up time was 3.6 years for GC users and 3.9 years for matched controls. The overall HR for death in oral GC users was 2.26 (95% CI 2.21-2.31). After exclusion of patients with malignant neoplasm, the HR for death was 1.41 (95% CI 1.38-1.45); 1.33 (95% CI 1.27-1.38) in single-occasion GC users (n=112,196), 1.36 (95% CI 1.30-1.42) in occasional users (n=63,862), 1.89 (95% CI 1.79-1.99) in medium-term users (n=19,129) and 1.67 (95% CI 1.51-1.84) in long-term users (n=7,191). The highest HRs were observed for deaths from heart failure (HR 1.71, 95% CI 1.63-1.80), sepsis (HR 1.71, 95% CI 1.51-1.94), and pulmonary embolism (HR 1.87, 95% CI 1.58-2.21).
Conclusion. GC users have excess mortality compared to the background population. This illustrates the importance of surveillance for patients on oral GC treatment where adverse effects should be monitored and, when indicated, appropriately treated.

Neuroendocrinology and Pituitary

NEUROENDOCRINE & PITUITARY PATHOLOGIES

Hair Cortisol Measurement: An Innovative Method for Diagnosis and Follow-Up in Patients with Cushing's Disease

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