Journal of the American Society of Hypertension 10(11) (2016) 881–890

Research Article

Changes in the renin-angiotensin-aldosterone system in response to dietary salt intake in normal and hypertensive pregnancy. A randomized trial

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Manuscript received June 6, 2016 and accepted October 9, 2016

Abstract

It was hypothesized that primary renal sodium retention blunted the reactivity of the renin-angiotensin-aldosterone system to changes in salt intake in preeclampsia (PE). A randomized, cross-over, double-blinded, dietary intervention design was used to measure the effects of salt tablets or placebo during low-salt diet in PE patients (n = 7), healthy pregnant women (n = 15), and nonpregnant women (n = 13). High-salt intake decreased renin and angiotensin II concentrations significantly in healthy pregnant women ($P < .03$) and in nonpregnant women ($P < .001$), but not in PE ($P = .58$), while decreases in aldosterone and increases in brain natriuretic peptid (BNP) were similar in the groups. In PE patients, uterine and umbilical artery indices were not adversely changed during low-salt diet. Creatinine clearance was significantly lower in PE with no change by salt intake. PE patients displayed alterations of plasma renin and angiotensin II in response to changes in dietary salt intake compatible with a primary increase in renal sodium reabsorption in hypertensive pregnancies. J Am Soc Hypertens 2016;10(11):881–890.

Keywords: Hypertension; plasmin; proteinuria.

Introduction

Preeclampsia (PE) is characterized by the onset of hypertension and proteinuria after 20 weeks of gestation. Renal abnormalities include glomerular endotheliosis, impaired renal sodium excretion,[1] and suppressed levels of circulating renin, angiotensin II (ANGII), and aldosterone compared to normal pregnancies.[2–6] Normal pregnancy is characterized by lower systemic vascular resistance, higher arterial compliance, and elevated plasma concentrations of renin, ANGII, and aldosterone. This increase in the renin-angiotensin-aldosterone system (RAAS) components mediates the expansion of extracellular and blood volumes typical for pregnancy compared to nonpregnant women.[7,8] In addition, a significant role of ANGII and aldosterone for normal placental development, and thus fetal perfusion, has been shown in rodents.[9–11] In light of a significantly increased interstitial versus plasma fluid volume ratio and hypertension with suppression of RAAS in patients with PE,[12,13] the RAAS is less likely to drive the changes. Brown et al[1] discovered that patients with PE on normal salt diet retained infused sodium more avidly than healthy pregnant on a low-salt diet. Moreover, in preeclamptic women, furosemide administration yielded less stimulation of plasma renin concentration.[14] These observations could be compatible with a primary renal hyperreabsorption of

Supplemental Material can be found at www.ashjournal.com.

The study was financially supported by The Danish Research Council for Strategic Research (grant no. 11-115861), The Region of Southern Denmark (grant no. 10 15756) and The Lundbeck Foundation (grant no. R129-A10618).

Conflict of interest: The authors declare that they have no conflict of interest.

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1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2016.10.001

sodium at a site distal to the thick ascending limb of Henle's loop resulting in subsequent suppression of RAAS. What might cause this apparent hyperreabsorption of NaCl when RAAS is suppressed? Distal tubular rate-limiting apical sodium transport proteins are the Na-Cl co-transporter and epithelial sodium channel (ENaC). PE is associated with injury to the glomerular barrier for protein,[15,16] and the degree of proteinuria correlates to disease severity and to perinatal morbidity.[17–21] PE patients display an abnormal presence of the zymogen plasminogen in the urine with a positive correlation to urinary albumin concentrations.[22–25] Active plasmin cleaves the apical exodomain of the γ-subunit of the ENaC, causing activation.[22,25–27] Abnormal activity of ENaC is sufficient to provoke salt-sensitive hypertension and RAAS suppression. Our previous studies on proteolytic activation of ENaC led to the present hypothesis that inappropriate distal Na^+ retention leads to RAAS suppression and hypertension in hypertensive pregnancies including PE. Since direct pharmacological testing with Na^+ transport blockers like thiazides and amiloride is not feasible during pregnancy, a randomized, double-blinded, cross-over, dietary intervention trial was designed to test the hypothesis indirectly. It was hypothesized that PE is associated with attenuated salt sensitivity of the RAAS and with increased salt sensitivity of blood pressure, compared to normal pregnancies and nonpregnant controls. The protocol included a standardized low-salt diet supplemented with salt or placebo tablets in randomized order for four consecutive days as well as collections of 24-h urine and measurements of blood pressure, kidney function, plasma concentrations of renin, ANGII, aldosterone and BNP, uterine artery flow, body weight, body fluid parameters, and cardiac index (CI).

Material and Methods

The study was conducted in the Department of Gynecology and Obstetrics at Aarhus University Hospital, Skejby, Denmark, in 2013–2015. It included three groups of participants. A group with PE patients (PE, n = 7), a group with healthy pregnant women (HP, n = 15), and a group with healthy nonpregnant women (NonP, n = 13) (Figure S1). PE patients were recruited when referred to the hospital. HP were recruited during routine antenatal visit at Skejby Midwife Centre. NonP were recruited locally. PE patients included singleton pregnancies in gestational weeks 28–38, determined by ultrasound, with PE. PE was defined by hypertension (office blood pressure > 140/90 mm Hg) and proteinuria ≥1+ on a urine dip stick test later than 20 weeks of gestation, in accordance with national guidelines.

HP included healthy, singleton pregnancies in gestational week 28–38 who did not take any regular medication and did not suffer from any known diseases and who had not previously suffered from PE. They were age matched with the PE women. Participants were ≥18 years and able to fully understand the study conditions. PE patients received antihypertensive treatment according to department guidelines independent of the present protocol.

All participants gave written informed consent.

The study was approved by the local ethics committee (Region of Central Denmark) (Project ID: 1-10-72-600-12) and the Danish Data Protection Agency (ID: 2007-58-0010). Registration at www.Clinicaltrials.gov was ensured with identification number NCT01828138. The principles of the Declaration of Helsinki are followed.

Experimental Protocol

All participants were studied according to a standardized protocol. On the trial day, they reported between 7:30 AM and 10 AM. Within the groups, blocks of four participants were randomly assigned to ingest a standardized low-salt diet (containing 50–60 mmol NaCl/24 hours) supplemented with NaCl tablets (172 mmol/24 hours) or placebo tablets for 4 + 4 days achieving high-salt (222–232 mmol/24 hours) and low-salt (50–60 mmol/24 hours) intake periods, in a cross-over design (Figure S2).

Randomization was double blinded and managed by the hospital pharmacy and delivered in closed envelopes. Allocation details are illustrated in the online supplement (Figure S1).

The diet was prepared by the hospital kitchen in collaboration with a clinical dietician. Salt content was tested independently by a commercial laboratory (Eurofins Steins Laboratory A/S, Holstebro, Denmark). Participants were allowed to drink water as desired. To assess compliance, 24-hour urinary sodium excretion (07:00–07:00) was determined on the days prior to investigation. Each patient agreed to respect following terms: no alcohol consumption and no smoking within 24 hours prior to the study day and no food intake from midnight before the tests.

Participants were advised not to practice hard physical activity during the dietary period. Blood pressure was measured after at least 10 minutes of rest in the seated position using blood pressure monitor ''microlife BP a100 plus'' (Microlife AG, Switzerland) in accordance with national guidelines and recommendations consistent with the European Society of Hypertension. The device fulfills validation recommendations of the international protocol for self-measurement.[28,29] Cardiac output (CO), extracellular volume (ECV), and intracellular volume (ICV) were measured noninvasively using a bioelectrical impedance device. More details are found in the Online Supplement together with details regarding flow measurements and blood sample analysis. Blood was collected by venipuncture after at least 20 minutes of rest in a seated position.

Statistical Analysis

Methodology to ascertain normally distributed data was used. If standard deviations differed significantly