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Salt, aldosterone and extrarenal Na^+ - sensitive responses in pregnancy

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ABSTRACT

Outside of pregnancy excessive salt consumption is known to be harmful being linked to increased blood pressure and cardiovascular disease. However, pregnancy represents a major change to a woman's physiology resulting in an intimate adaptation to environmental conditions. It is now becoming apparent that salt is essential for a number of these changes during pregnancy including haematological, cardiac adaptations as well as directly influencing placental development and the uteroplacental immune environment. The present review discusses the important role that salt has during normal pregnancy and evidence will also be presented to show how the placenta may act as a salt sensing organ temporarily, yet substantially regulating maternal blood pressure.

1. The physiological need for salt during pregnancy

The role of excessive dietary salt (sodium chloride, NaCl) in causing hypertension, cardiovascular disease and stroke is now well established [1]. However, sodium is also essential for healthy physiological function as it is required for the regulation of fluid levels, temperature and pH. The recommended level of dietary salt intake is 5 g per day, which equates to around 2000 mg of Na^+ [2], however dietary salt intake is above this recommended daily amount in a majority of countries [3]. As blood pressure responses in a healthy population follows a Gaussian distribution [4], very low levels of salt intake may even stimulate pressure responses of the renin angiotensin II system (RAS) [5].

In pregnancy dietary salt intake seems to facilitate the numerous physiological changes that must occur to support the growth and development of the placenta and foetus. These changes affect every organ system in the body and begin shortly after conception [6] (see Table 1). For the majority of women these changes resolve following parturition with no long term residual effects. However, for certain pathological conditions, for example the hypertension present in pre-eclampsia, it may take much longer for pre-pregnancy physiologically normal levels to return.

Haematological changes are an important part of the maternal physiological response to pregnancy. Blood volume increases gradually during pregnancy by approximately thirty to fifty percent and this is proportional to the birthweight of the baby. The expansion in plasma volume is greater than the increase in erythrocyte cell number. The increase in plasma volume is crucial for maintaining circulating blood volume, blood pressure and uteroplacental perfusion during pregnancy. Plasma volume expansion is brought about by increased salt and thirst appetite combined with activation of the RAS. In close interaction, angiotensin II and to a large extent VEGF stimulate aldosterone and subsequent salt and water retention in the kidneys [7,8]. Sodium retention occurs at a rate of approximately 2–6 mmol Na^+ per day [9] resulting in increased total body sodium of around 1000 mEq [10] as plasma osmolality falls [11,12] by 10 mosmol/kg below non-pregnant levels [11,13]. Increased activity of the RAS is mediated by not only an increased production of renin by the kidneys but also renin production by the ovaries and the uteroplacental unit which produce an inactive precursor protein of renin during early pregnancy [14]. Yet, in contrast to non-pregnant women in pregnancy angiotensinogen secretion from the liver driven by placental production of oestrogens results in proportionally increased levels of aldosterone. Plasma levels of aldosterone correlate well with those of oestrogens and rise progressively during pregnancy [15]. Natriuresis still

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Table 1
Physiological changes that occur during normal human pregnancy.

Body system	Physiological adaptation to pregnancy
Haematological	Plasma volume expansion occurs to around 50% of pre-pregnancy volume. However, red blood cell volume increases by only 20–30% resulting in a fall in haemoglobin concentration, haematocrit and red blood cell count [63,64].
Cardiovascular	Large increase in cardiac output from early pregnancy onwards [65]. Peripheral vasodilation results in a fall in systemic vascular resistance which is compensated for by increased stroke volume and also (but to a lesser extent) an increase in heart rate [66].
Renal	There are increases in both renal blood flow by around 50% and glomerular filtration rate (GFR) by between 30 and 50% which results in an increase in the fractional excretion of protein by up to 300 mg/day. Increased renal blood flow leads to an increase in renal size of 1–1.5 cm [67,68]. Activation of the renin-angiotensin system (RAS) leads to increased plasma levels of both renin and aldosterone and subsequent salt and water retention in the distal tubule and collecting duct. However there is dissociation between plasma concentrations of renin and aldosterone during pregnancy. Increases in aldosterone concentrations from pre-pregnancy values are proportionally greater than those of renin by the third trimester [7,69].

occurs despite the sodium retaining properties of aldosterone due to the potent antagonist actions of progesterone and the rise in glomerular filtration rate which allows excretion of excess sodium. Furthermore, progesterone acts to inhibit kaluresis thereby ensuring that potassium excretion is kept constant throughout pregnancy [16,17]. In pre-eclampsia however plasma volume expansion is reduced and plasma volume does not reach the same levels as seen in normotensive pregnancy [18]. Those women destined to develop later preeclampsia lose more of a given sodium load then those with a regular pregnancy outcome suggesting a beneficial effect of limiting excess natriuresis [19].

2. Salt-sensing: the role of the immune system

The observation in astronauts on board the MIR space station of sodium storage in the skin without accompanying water retention has led the way in extrarenal sodium storage being accepted as part of normal healthy physiology [20–22]. Furthermore evidence has shown that blood pressure regulation can be influenced by the sodium retained in the subdermal interstitium by mechanisms which involve the immune system. The first of these mechanisms is via upregulated expression of interleukin 17 (IL-17) which has been shown to increase the formation of reactive oxygen species and inflammatory leucocytes within the circulation resulting in endothelial dysfunction and raised systolic blood pressure. Sodium is implicated for this process as high salt concentrations stimulate the development of IL-17 producing $CD4^+$ T helper cells, known as Th17 cells [23]. The mechanism by which salt is able to induce Th17 polarisation by T lymphocytes is via p38/MAPK and NFAT5 as well as serum/glucocorticoid-regulated kinase 1 (SGK-1) dependent signalling [23,24].

SGK-1 is also important in salt sensing and responding to changes in extracellular Na^+ [25]. Excess production of glucocorticoid or mineralocorticoid, inflammation and hypertonicity all cause upregulation of SGK-1 and this in turn leads to increased activity of a number of ion channels including the epithelial sodium channel (ENaC) [26]. Excessive expression and activity of SGK-1 promotes vascular remodelling and macrophage activation which results in worsening of the pathophysiological processes associated with hypertension, diabetes, tumour growth and infertility [27,28]. SGK-1 knockout mice when treated with excess mineralocorticoid and high salt show no progression of hypertension. The exact mechanisms by which SGK-1 is involved in hypertension and cardiovascular disease remains to be fully elucidated however they may involve regulation of the transcription factors forkhead transcription factor 3a, beta-catenin and nuclear factor κ B [29–31].

Tissue macrophages are also important in extrarenal sodium mediated regulation of blood pressure. Following a high salt diet excess Na^+ is bound in an osmotically inactive form by negatively charged polyanionic glycosaminoglycans present in the skin interstitium. Macrophages actively migrate to areas of hypertonic sodium storage, leading to the suggestion that these cells are mobile osmoreceptors [32]. High levels of sodium result in macrophage expression of tonicity-responsive enhancer binding protein (TonEBP). TonEBP is an osmosensitive transcription factor with a wide range of roles. One of the key roles of TonEBP with regard to blood pressure regulation is that it is able to bind to two sites within the vascular endothelial growth factor C (VEGF-C) promoter and is thus able to regulate VEGF-C expression. VEGF-C released by the macrophages results in increased lymphangiogenesis of pre-existing lymph capillaries by binding VEGFR3 receptors. This enhances the lymph-capillary network in the skin facilitating the clearance of salt [33]. Release of VEGF-C triggers increased endothelial nitric oxide synthase (eNOS) expression via activation of VEGFR2 receptors. The potent vasodilator activity of nitric oxide produced in this manner acts to compensate blood pressure following a high salt diet. VEGF-C release is also able to stimulate induction of Th17 lymphocytes [34]. Reduction in VEGF-C availability via either reduced macrophage numbers or binding to its soluble receptor VEGFR3 leads to augmented interstitial hypertonic volume retention resulting in decreased eNOS expression culminating in increased blood pressure [33]. Intradermal sodium sensing is not suggested to overrule renal regulatory function but rather act in a complementary manner to assist with electrolyte balance, volume regulation and blood pressure control [35].

Salt is also able to regulate the switching of macrophages between their M1 pro-inflammatory and M2 anti-inflammatory phenotypes via salt-inducible kinase (SIK) activity. Inhibition of SIKs promotes an M2 phenotype via IL-10 production. A similar induction of an anti-inflammatory phenotype is also observed in SIK inhibitor treated dendritic cells. The role of SIK in regulating pro-inflammatory and anti-inflammatory cell lineage is limited only to myeloid derived cells and it is unable to influence T lymphocyte development due its signalling pathway which is regulated by MAP kinase pathways rather than the PKA pathways involved in myeloid cell differentiation.

3. The importance of endogenous ouabain

The molecular mechanisms by which salt induces the changes that lead to hypertension are unknown. Furthermore the ability of salt to alter blood pressure varies between individuals and is referred to as salt-sensitivity. One candidate molecule which may have a key role in linking salt with hypertension is endogenous ouabain (EO). In high salt intake of salt-sensitive individuals this endogenous cardiotonic steroid is secreted by the adrenal glands and the hypothalamus following elevation of plasma and cerebrospinal fluid Na^+. It is this salt induced secretion of EO that is believed to be central to salt induced hypertension. The relationship of EO with Na^+ is complex but both correlate with blood pressure [36]. The way in which EO is able to regulate blood pressure is due to its ability to function as a Na^+ pump inhibitor thereby

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