

Editorial Comment

Antenatal excessive sodium intake induces adverse vascular remodelling in offspring

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There is accumulating evidence from human studies [1, 2] that high salt intake is an important contributor to the development of hypertension and subsequent adverse cardiovascular events. The kidneys have been identified as key players in the functional disturbances that link salt intake to the arterial blood pressure, but the primary renal defects are still unresolved. Subtle microvascular or tubulointerstitial kidney injury has been proposed as the major underlying cause of defects in renal sodium excretion, which results in hypertension [3]. The pivotal role of kidney injury in the pathogenesis of hypertension has been shown in elegant clinical studies performed by Curtis *et al.* [4] who showed normalization of the blood pressure upon renal transplantation in hypertensive patients with end-stage renal disease. Further evidence for the central role of the kidneys in the pathophysiology of hypertension comes from genetic studies in families with a high prevalence of severe hypertension that identified several mutations in genes encoding for proteins involved in renal salt handling, such as ion channels and transporters [5]. In line with the latter observation, most experts in the field of hypertension agree that an increase in extracellular fluid volume is the central mechanism that links salt handling in kidneys with increased blood pressure [6]. A chronic high-salt diet might also raise peripheral vascular resistance, most likely mediated by increased levels of circulating endogenous Na⁺-K⁺-ATPase inhibitors [7] including cardiotonic steroids such as marinobufagenin (MBG), which is synthesized in the adrenal glands [8]. In addition to the role of MBG in the induction of compensatory natriuresis upon salt loading [9], MBG is thought to enhance vascular tone by increasing cytosolic Ca²⁺ concentration and contractility of vascular smooth muscle cells (VSMCs) in the arterial wall [10].

Previous studies have already shown that high salt intake of rat dams during pregnancy, lactation and weaning caused persistent hypertension in the offspring once they reached adulthood [11]. The question is, do the detrimental effects on vasculature from a high dietary sodium intake precede the development of hypertension.

In an interesting paper [12] published in the present issue of *NDT*, Dr Piecha *et al.* addressed this issue by evaluating the morphological effects on the vasculature of offspring after high salt intake of rat dams during pregnancy. For this purpose, Sprague-Dawley rats were fed a standard rodent diet with a low-normal (0.15%) or high (8.0%) salt content during pregnancy and lactation. Obviously, the investigators choose for an experimental set-up with extreme sodium loading since 8% salt content of ± 500 g of food during pregnancy in rats, corresponds with 200 g of sodium/day for a human adult of 75 kg. After weaning at 4 weeks of age, offspring were maintained on the same diet or switched to high- or low-salt diet, respectively. The vascular geometry was assessed in the male offspring at 7 and 12 weeks after birth. The wall thickness of central arteries appeared significantly larger in the offspring of dams on a high-salt diet, irrespective of the post-weaning diet. Detailed histological analysis of these arteries revealed that collagen (as hallmark of fibrosis) was the main constituent responsible for this larger wall thickness. In contrast, offspring from dams that were exposed to low salt during pregnancy did not show any signs of fibrosis within the arterial wall. In addition, blood pressure was not different between the groups of offspring, nor between the groups of dams at the end of pregnancy. The lack of effect of high salt intake during pregnancy on blood pressure in the offspring is remarkable, although Porter *et al.* [13] obtained similar results in previous studies. Interestingly, the latter study did reveal an increased blood pressure response to stress in the offspring. Apparently, the fibrotic response in the vasculature is not extensive enough to cause clear haemodynamic effects under baseline conditions within the evaluated time frame of 12 weeks after birth.

How should we then interpret the blood pressure-independent effect of dietary sodium intake during pregnancy on the vasculature of the offspring? The present study does not completely clarify whether the effect of salt is mediated via plasma sodium concentration, positive sodium balance or indirectly via salt-induced hormonal

changes. Indeed, the authors did not measure plasma sodium concentrations in the dams nor in the offspring during pregnancy. Although the plasma sodium concentration usually does not change upon increased (oral) sodium intake, the offspring could still have been exposed to a higher sodium load because the high sodium intake of the dams might have affected placental perfusion or amniotic fluid sodium concentration. To exclude sodium loading of foetuses as the potential cause of vascular fibrosis, the authors should have included measurements of foetal total body sodium.

Alternatively, salt-induced hormonal changes could have mediated the observed vascular fibrosis in the offspring. The investigators suggest a causative role for cardiotoxic steroids, in particular MBG. They measured circulating levels of MBG and showed a 2-fold increase at Week 12 in the offspring of mothers on a high-salt diet, independent of the offspring's current sodium intake. They also show a concomitant increase in the vascular oxidative stress, reflected by enhanced nitrotyrosine staining within the vessel wall. Recent studies in a rat model of pre-eclampsia also suggest that MBG stimulates oxidative stress, which could be prevented by resibufogenin, a competitive inhibitor of MBG [14]. Furthermore, treatment with a monoclonal antibody against MBG has been shown to reverse cardiac fibrosis in rats with chronic renal failure [15]. Circumstantial evidence for the role of MBG-

induced oxidative stress as the driving force for vascular fibrosis in hypertension comes from previous studies in adult humans and rats, which demonstrated that excess sodium intake is associated with increased circulating levels of MBG [16] and enhances oxidative stress and collagen deposition in the vascular wall [17, 18]. What could be the mechanism that links MBG to oxidative stress in the vessel wall? In a recent elegant review on the (patho)physiological role of MBG [10], Dr McCarty hypothesized that the inhibition of endothelial sodium pump activity by MBG could promote membrane depolarization, which has been shown to provoke NADPH oxidase-mediated oxidative stress and impaired nitric oxide synthase (NOS) activity in endothelial cells [19]. In their study, Dr Piecha *et al.* indeed observed decreased aortic expression of NOS and increased plasma levels of asymmetric dimethylarginine (an endogenous competitive inhibitor of NOS) in the offspring of dams on a high sodium diet. Moreover, the expression of the nitric oxide receptor in the vasculature—soluble guanylate cyclase (sGC)—was significantly lower in the offspring of mothers on a high-salt diet. Previous studies in Dahl-salt sensitive rats have provided evidence for a causal link between sGC and fibrotic remodelling [20].

Unfortunately, the lack of direct interventions in MBG and sGC pathways preclude final conclusions on the

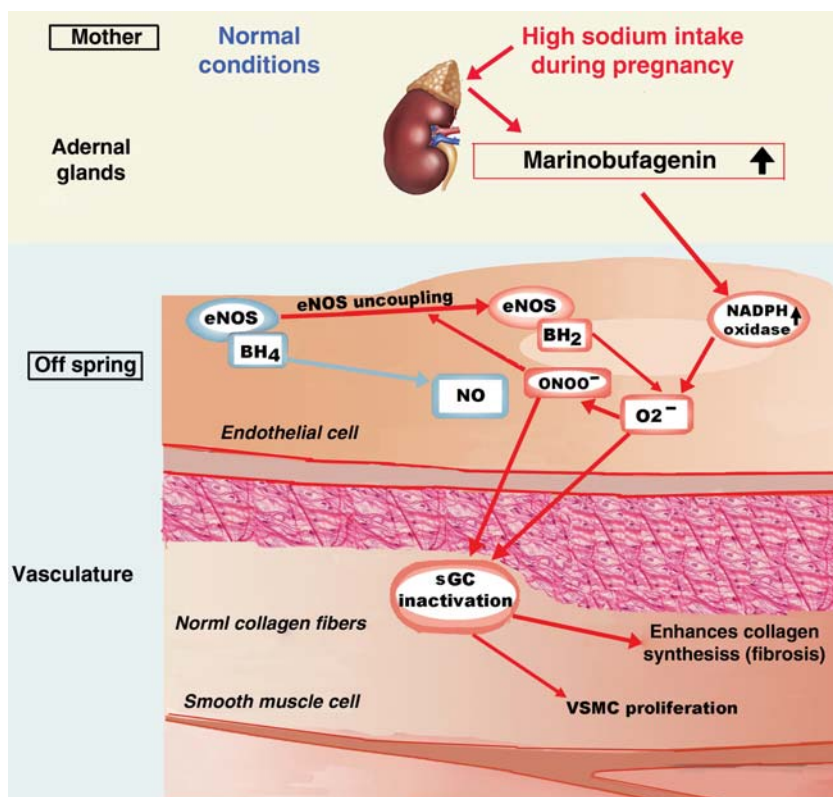


Fig. 1. Potential mechanisms underlying the fibrotic response in the vasculature in the offspring of dams that are exposed to high salt during pregnancy. High sodium intake during pregnancy increases plasma levels of MBG that is synthesized in the adrenal glands. This results in NADPH-mediated production of superoxide and peroxynitrite in endothelial cells of the offspring vasculature. The latter (mediated by lack of availability of the cofactor BH₄) induces uncoupling of eNOS, O₂⁻/ONOO⁻ production and downstream inactivation of sGC in VSMCs. This process leads to disturbed homeostasis resulting in increased proliferation of VSMCs and enhanced collagen synthesis. Abbreviations: BH₄, tetrahydrobiopterin; BH₂, dihydrobiopterin; sGC, soluble guanylate cyclase; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; O₂⁻, superoxide; ONOO⁻, peroxynitrite; VSMC, vascular smooth muscle cell.

mechanisms (Figure 1) that are responsible for increased vascular fibrosis in the offspring of dams with a high sodium intake during pregnancy. Nevertheless, this paper could have important clinical consequences if these observations can be extrapolated to humans. Indeed, this adverse foetal programming of the vasculature could ultimately lead to thickening and increased stiffness of the arterial wall which goes hand-in-hand with an increased cardiovascular risk. Once the causative role of MBG in vascular fibrosis upon sodium intake is unravelled in future studies, it may also open up new therapeutic avenues in the treatment of hypertension. Finally, additional clinical studies with relevant clinical end points are needed to determine the optimal salt intake for pregnant women, because evidence for any advice to alter salt intake during pregnancy is lacking [21].

Conflict of interest statement. None declared.

(See related article by Piecha *et al.* High salt intake causes adverse fetal programming—vascular effects beyond blood pressure. *Nephrol Dial Transplant* 2012; 27:3464–3476.)

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