Clinical impact of nonosmotic sodium storage

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CHAPTER 10

Summary and Perspectives
SUMMARY

CHAPTER 1 provided an introduction for this thesis in which we discuss the relevance of adequate blood pressure (BP) control and low sodium intake. High sodium intake is causally related to high BP and high BP is known to increase the risk for cardiovascular events and death considerably. In the Western world an average of 4-5 grams of sodium is consumed daily (10-12.5 grams of salt). This is in sharp contrast with the sodium intake of 2 grams that is recommended by the World Health Organization (WHO). The effect of sodium intake on BP varies considerably among individuals, discriminating sodium sensitive individuals, who are characterized by a BP increase after an increase in sodium intake, from sodium resistant individuals, who do not develop a BP increase.

We also discussed the current views on the physiology of sodium homeostasis. According to the two-compartment model, the kidney is solely responsible for matching sodium excretion and sodium intake, thereby preventing sodium and water retention, extracellular volume expansion and an increase in BP. The kidney is therefore thought to play a pivotal role in determining the effects of sodium intake on BP (i.e. sodium sensitivity).

This theory has been questioned by long-term sodium balance studies that have shown that sodium can accumulate in the human body without concurrent retention of water. This is not in line with the current physiological concept that sodium retention is always accompanied by water retention. Experimental studies have demonstrated that negatively-charged polysaccharides, called glycosaminoglycans, are able to bind and osmotically inactivate sodium in the skin interstitium. As a result, sodium storage by glycosaminoglycans will not be accompanied by water retention. Skin sodium accumulation has been observed in patients that are prone to volume expansion such as patients with hypertension, heart failure, hyperaldosteronism and dialysis patients and may affect BP regulation.

In CHAPTER 2 we introduce our main hypothesis that nonosmotic sodium storage has a significant impact on sodium and water homeostasis. We also discuss the potential role of the endothelial surface layer (ESL) in sodium and water homeostasis. The ESL is a dynamic layer that covers the inner surface of all blood vessel throughout the body and is in continuous contact with the circulation. It consists of glycosaminoglycans, proteoglycans, glycoproteins and adsorbed plasma proteins. Considering the large systemic volume of the ESL of 1.5 liter and the sodium binding properties of glycosaminoglycans, non-osmotic sodium storage by endothelial glycosaminoglycans may help to prevent sodium induced volume overload and hypertension. A damaged ESL, on the other hand, which is among others seen in diabetic and chronic kidney disease patients, may contribute to the disturbed volume regulation and high BP that is often
observed in these patients. Restoration of the ESL in these patients may increase non-osmotic sodium storage capacity and help to control BP and prevent volume overload.

In **CHAPTER 3** we investigated sodium and water homeostasis in mice with defective glycosaminoglycans. Heparan sulfate is the most abundant glycosaminoglycan in the ESL and is present in high concentrations in the dermo-epidermal junction of the skin. Exostosin glycosyltransferase 1 and 2 (EXT1 and EXT2) genes are responsible for polymerization of heparan sulfates and heterozygous loss of these genes has been shown to result in shorter heparan sulfate chains. In line with these findings we observed that mice with heterozygous loss of EXT1 and EXT2 (EXT1-2+/−) had an 80% reduction in ESL thickness. As a result, these mice may have less capacity for non-osmotic sodium storage. We observed that mice with defective heparan sulfate polymerization had abnormal sodium and water homeostasis. Relative to wildtypes, EXT1-2+/− mice had a decreased skin sodium and water content, higher heart rate, increased plasma osmolality and an increased fluid intake suggesting dehydration and volume depletion. In addition, EXT1-2+/− mice had endothelial dysfunction. After high sodium intake, skin sodium and water content of EXT1-2+/− mice increased significantly and heart rate decreased whereas no change was observed in wildtypes. Also, we observed an increase in skin glycosaminoglycan content in EXT1-2+/− mice. BP was not affected by high sodium intake in both groups. The decrease in heart rate and increased skin glycosaminoglycan content may have prevented a BP increase in EXT1-2+/− mice. Acute hypertonic NaCl infusion did result in a different BP response. Whereas BP showed a normal physiologic decrease in wildtypes, BP increased in EXT1-2+/− mice. Together, these data demonstrate that heparan sulfate glycosaminoglycans are crucial for normal sodium and water homeostasis, ESL structure and function, and may be able to prevent sodium induced volume expansion.

In **CHAPTER 4** we conducted a short-term sodium balance study after hypertonic NaCl infusion in healthy volunteers. We examined whether the observed changes of plasma sodium concentration after saline infusion were in line with the changes that were expected according to the Adrogue-Madias and Nguyen-Kurtz formula. These formulas are widely implemented in the clinical setting to predict changes in plasma sodium concentration following infusion therapy in dysnatremic patients. However, both formulas are based on the classical two-compartment model and do not take into account non-osmotic sodium storage in the skin or ESL. Considering the volume of the skin interstitium and ESL, non-osmotic sodium storage may significantly affect sodium homeostasis. After infusion of hypertonic NaCl in 12 healthy volunteers we observed significant differences between changes in plasma sodium concentration that were measured and the changes that were expected according to the Adrogue-Madias and Nguyen-Kurtz formula. Two and four hours after infusion, the observed plasma sodium
concentration was on average 2 mmol/L different from the predicted values. Conversely, these formulas can be used to estimate the expected urinary cation excretion (sodium and potassium) following a certain decrease in plasma sodium concentration. However, of the 108 mmol of osmotically active cations that had been cleared from the body water during a four-hour follow-up we were only able to retrieve 50% in the urine. These results demonstrate that non-osmotic sodium storage significantly affects short-term sodium homeostasis in healthy individuals. These subject may either have a residual capacity for non-osmotic sodium storage or may be able to create such a capacity within four hours, to store sodium in situations of sodium excess. Moreover, these results may provide an explanation for the inaccuracy of the Adrogue-Madias and Nguyen-Kurtz formula that is often observed in the clinic when treating dysnatremic patients. Frequent laboratory follow-up of plasma sodium concentration after initiation of treatment is therefore essential to prevent inadequate treatment or overcorrection of dysnatremias.

The existence of the above described ‘third compartment’ in which sodium can be (temporarily) stored may have significant consequences for sodium excretion. This is in conflict with the assumption of the two-compartment model that 24-hour sodium excretion equals 24-hour sodium intake during steady state sodium intake. Indeed, long-term sodium balance studies have shown that 24-hour sodium excretion can be up to 100 mmol (~6 grams of salt) different from sodium intake during steady state. Nevertheless, many cohort studies have used a single 24-hour urine collection to estimate sodium intake for investigation of the relation between sodium intake and long-term outcome. In CHAPTER 5, we tested whether estimation of individual sodium intake and its associated cardiovascular and renal risk is different when sodium intake is estimated with multiple 24-hour collections that are obtained during follow-up, instead of using a single baseline collection. In a cohort of 574 outpatient subjects with almost 10,000 24-hour urine collections we found that population sodium intake was similar when assessed at baseline or during 1, 5 or 15-year follow-up. However, estimates of individual sodium intake changed >34 mmol (2 grams of salt) in half of the subjects when using multiple follow-up collections instead of a single baseline collection. As a result, 50% of the subjects switched between tertiles that were based on sodium intake. Consequently, the observed relation between sodium intake and long-term outcome changed significantly. Hazard ratios for cardiovascular and renal outcomes were up to 85% different when sodium intake was not estimated at baseline but during follow-up. These changes in hazard ratio were observed both when sodium intake was estimated within 1 year after baseline as well as when 5-year averages were used to estimate sodium intake. The results of previous cohort studies that have used a single baseline measurement to estimate sodium intake and assess the relation between sodium intake and long-term outcome may therefore be much different if sodium intake was estimated using (multiple)
samples obtained during follow-up. Data from these studies should therefore be interpreted with caution.

In CHAPTER 6 we assessed whether restoration of the ESL results in improved BP control. We performed a meta-analysis of previous studies that investigated sulodexide for any medical condition. Sulodexide is an orally available drug that consists of heparan sulfate (80%) and dermatan sulfate (20%) glycosaminoglycans and has previously shown to restore ESL thickness in patients with a damaged ESL. In our analysis, we selected studies that had also measured BP. The majority of studies were performed in patients with diabetic nephropathy that were treated with renin-angiotensin-aldosterone system (RAAS) inhibitors as well as other antihypertensive drugs. As a result, BP was well-controlled in most patients at baseline. Nevertheless, we observed a slight BP reduction in these patients after sulodexide treatment. In two studies that included patients with uncontrolled BP at baseline, which had an actual indication for antihypertensive treatment, we observed large systolic (10 mmHg) and diastolic (5 mmHg) placebo-subtracted BP reductions that were similar to the effects of regular antihypertensive drugs. Considering the fact that sulodexide’s working mechanisms differs from regular antihypertensive drugs, and may decrease sodium sensitivity, sulodexide may be an interesting option for treatment of hypertension.

In CHAPTER 7 we analysed individual patient data of the Sun-MICRO and Sun-MACRO study to determine which patients would benefit most from sulodexide treatment in terms of BP control. Both randomized, placebo-controlled, double-blind studies have investigated the effect of sulodexide on albuminuria in patients with micro-albuminuria and macro-albuminuria, respectively. Previous studies have demonstrated that ESL thickness decreases with increasing amounts of albuminuria. We therefore hypothesized that sulodexide would have the largest beneficial effects on BP in patients with the highest degree of albuminuria. Our post-hoc analysis demonstrated that baseline albuminuria was an important modifier of the BP response to sulodexide. In micro-albuminuric patients we observed no difference in BP response between sulodexide and placebo groups. However, in macro-albuminuric patients we observed a significantly different BP response between both groups. In patients with an albumin-creatinine ratio >1,000 mg/g, sulodexide resulted in a 5 mmHg BP decrease compared to placebo. The fact that this BP decrease was observed while the average baseline BP was well-controlled suggests that the antihypertensive effect may be larger in patients with uncontrolled BP. The data of this post-hoc analysis substantiate the hypothesis that the BP lowering effect of sulodexide is due to restoration of the ESL.
Besides the ability for non-osmotic sodium storage, the ESL protects the vascular wall against development of atherosclerosis, inflammation and thrombosis. In **CHAPTER 8** we investigated whether ESL dimensions may be used to estimate individual cardiovascular risk. We compared the ESL dimensions of healthy volunteers, patients with low and high cardiovascular risk, and patients that had a history of a cardiovascular event. We assessed ESL dimension with sidestream dark field (SDF) imaging and Glycocheck® software, an experimental technique that measures the outside layer of the ESL indirectly by assessing to which extent passing red blood cells are able to compress the ESL. This study demonstrated that ESL status, as measured with this technique, is not associated with cardiovascular risk. In addition, we did not observe any association with individual cardiovascular risk factors such as dyslipidemia, hypertension, obesity or diabetes. This indicates that ESL measurements with SDF imaging and Glycocheck® software do not contribute to risk stratification for cardiovascular disease. As this experimental technique has limitations and only images the sublingual microcirculation, it is currently unknown whether systemic ESL volume may be related to cardiovascular risk.

In **CHAPTER 9** we investigated whether BP control may be improved by optimization of current antihypertensive treatment strategies that affect the sodium balance. Thiazide diuretics are recommended for first-line antihypertensive treatment by guidelines and prescribed to approximately one million patients in the Netherlands. Thiazide diuretics can be separated in thiazide-type diuretics that are prescribed to 90-95% of all patients, such as hydrochlorothiazide, and thiazide-like diuretics, such as chlorthalidone. Considering the longer elimination half-life and possible pleiotropic effects of thiazide-like diuretics on platelet function and vascular permeability, we assessed whether thiazide-like diuretics may be superior to thiazide-type diuretics in prevention of cardiovascular events. As no direct comparisons between both classes are available, we meta-analysed studies that compared thiazide-type and thiazide-like diuretics with placebo or other antihypertensive treatments. This analysis, which included over 480,000 patient years, demonstrated that, for a given BP reduction, thiazide-like diuretics were superior in prevention of cardiovascular disease and heart failure. Relative to thiazide-type diuretics, thiazide-like diuretics decreased cardiovascular events and heart failure with 12% and 21%, respectively. The incidence of adverse events was equal in both groups. We were not able to assess whether these beneficial effects of thiazide-like diuretics were the result of pleiotropic effects or improved 24-hour BP control that were not detected by the included studies that relied on office BP measurements. Although these results were derived from an indirect comparison, it represents the best evidence that is currently available. As the majority of patients are currently being treated with thiazide-type diuretics that seem to be inferior to thiazide-like diuretics, large health benefits may be achieved by switching to thiazide-like diuretics.
**PERSPECTIVES**

This thesis demonstrates that sodium and water homeostasis is far more complicated than previously assumed. We have demonstrated that the presence of a third compartment, in which sodium can be stored without concurrent water retention, has a significant impact on daily clinical practice. The involvement of this compartment may provide new opportunities for therapeutic interventions in patients with dysnatremias, hypertension and volume overload.

**Treatment of dysnatremic patients**

These new insights in sodium homeostasis may help to improve treatment strategies for hypotensive and hypernatremic patients. To correct the plasma sodium concentration, such patients are treated with hypotonic, isotonic or hypertonic saline infusion. In chapter 4 we demonstrated that the current formulas, which are based on the two-compartment model and do not take into account nonosmotic sodium storage in a third compartment, are not able to estimate the amount of infusion that is needed for correction of plasma sodium concentration. This may be potentially dangerous as overcorrection or undertreatment may lead to serious complications and possibly death.

To optimize the Adrogue-Madias formula, we need to determine the exact contribution of non-osmotic sodium storage in the skin interstitium and ESL. In recent years, multiple studies have used magnetic resonance imaging (MRI) of sodium to quantify skin sodium content\textsuperscript{1-4}. These studies have demonstrated that skin sodium content depends on gender, age and blood pressure, and is increased in patients with volume overload\textsuperscript{1-3}. Skin sodium content is also affected by treatments that are currently used in daily practice. Diuretic therapy in heart failure patients as well as hypotonic fluid and desmopressin administration in a hypernatremic patient and dialysis in kidney failure patients have been shown to decrease skin sodium content\textsuperscript{1,2,5).

Considering the potential role of endothelial GAGs in sodium homeostasis, the ESL volume is one of the parameters that may be of additive value to the current formulas. However, estimation of ESL volume is complex. Previously, ESL volume was measured by subtracting the volume of circulating labelled red blood cells, infused, from the total intravascular volume, as measured by infusion of an ESL permeable tracer. These measurements were reproducible and demonstrated an ESL volume of 1.5 L in healthy individuals, which decreased to 0.2 L in diabetic patients with macroalbuminuria\textsuperscript{6,7}. However, these invasive and time-consuming methods are not suitable for estimation of ESL volume in large cohorts or daily clinical practice. Furthermore, ESL thickness has been estimated using Glycocheck® software and sidestream dark field imaging of the sublingual microcirculation\textsuperscript{8-10}. However, this is an indirect technique in which only the most outer part of the ESL, called perfused boundary region, is measured. The exact
contribution of the perfused boundary region to the entire ESL volume, and whether this may be different among diseases or subjects, is currently unknown. Also, measurement may be different from systemic ESL status and may be affected by haematocrit and BP. These unknown factors complicate interpretation of estimates of ESL volume by the Glycocheck® software.

Regardless of whether nonosmotic sodium storage capacity can be estimated accurately, it is complex to implement these new variables in the current formulas. Nonosmotic sodium storage in the skin as well as ESL volume are regulated by a number of factors such as diet, blood pressure, gender, age and co-morbidities like diabetes and/or renal insufficiency. We therefore need new research to understand the contribution of nonosmotic sodium to sodium homeostasis and to put these data into clinical practice.

**Antihypertensive treatment with sulodexide**

This thesis demonstrates that sulodexide, an orally available drug that is able to restore ESL thickness, decreases BP in hypertensive patients. The magnitude of this BP response is similar to the decrease in BP that is seen after treatment with regular antihypertensive drugs. In addition, sulodexide has been shown to decrease the number of recurrent venous thromboembolisms and have an anti-inflammatory and lipid-lowering effect. Considering the high cardiovascular risk of most hypertensive patients, these additional capacities of sulodexide may help to improve cardiovascular risk beyond BP. Also, sulodexide seems patient-friendly as the incidence of adverse events does not differ from placebo.

Although the exact mechanism is unknown, the beneficial effects of sulodexide on BP seem to be the result of an improved ESL function. As a result of ESL restoration nonosmotic sodium storage capacity increases and endothelial function improves. As this working mechanism is different from regular antihypertensive drugs, sulodexide may be of additive value to the current antihypertensive treatment strategies and help to improve BP control, which is much needed. Despite antihypertensive treatment, 50% of patients with hypertension have an uncontrolled BP. Too much sodium consumption is one of the primary causes of difficult-to-treat hypertension. Besides the fact that increased sodium intake directly increases blood pressure, high sodium intake reduces the effect of the current antihypertensive drugs considerably. By increasing non-osmotic sodium storage capacity sulodexide may not only decrease BP directly but may also potentiate the efficacy of other antihypertensive drugs. Besides high sodium intake, non-compliance is an important cause of uncontrolled BP. Side effects of the current antihypertensive drugs are one of the main reasons for non-compliance. The favourable side effect profile of sulodexide may increase treatment compliance compared to regular antihypertensive drugs, which may improve BP control. So far, direct comparisons of sulodexide with other antihypertensive drugs are lacking.
Patients with volume overload such as dialysis patients or patients with heart failure may also benefit from sulodexide treatment. By osmotic inactivation of sodium, sulodexide may decrease edema leading to less symptoms and hospitalisations for volume overload. A previous study from 1994, in which the anti-thrombotic effects of sulodexide after myocardial infarction were tested, supports this hypothesis. In this study, sulodexide significantly decreased the incidence of heart failure compared to placebo while there was no concurrent decrease of the re-infarction rate. At that time, these inexplicable findings did not seem to be the result of an improved anti-thrombotic effect but may possibly be caused by improved BP control. Sulodexide is therefore an interesting drug to consider for future therapy in patients with volume overload.

The ESL and skin sodium content
Increased skin sodium content has mainly been observed in subjects that are prone to develop sodium sensitive hypertension such as patients with heart failure, dialysis or hyperaldosteronism. In addition, men had a higher skin sodium content compared to women and an increase in skin sodium accumulation was observed with increasing age. In general, the kidneys of such sodium sensitive individuals have plenty of capacity to excrete the excess of sodium. Nevertheless, the kidneys do not excrete the excess of sodium and BP increases subsequently. In sodium sensitive individuals, the defective sodium homeostasis may therefore not be caused by the kidney. Instead, the skin may play an important role as significant amounts of sodium can be present in the skin interstitium. The inability to mobilize sodium from the skin interstitium may impair renal sodium excretion and increase BP. In addition, increased skin sodium content may induce vasoconstriction and increase BP directly.

Experimental studies have demonstrated that macrophages play an important regulating role in nonosmotic skin sodium storage. Macrophages are known to migrate towards areas with high sodium concentrations such as the skin interstitium. The increased skin sodium concentration activates ‘tonicity-responsive enhancer binding protein’ (TonEBP) in macrophages. As a result the macrophages start to produce ‘vascular endothelial growth factor C’ (VEGF-C). Subsequently, VEGF-C induces proliferation of lymph vessels, which have been shown to be responsible for transportation of sodium from the skin back to the systemic circulation. Dysfunction of this system has been shown to induce skin sodium accumulation and sodium sensitive hypertension. Consequently, the kidney is not able to excrete the excess of sodium that is retained in the skin despite a normal kidney function.

The ESL is strategically located on the luminal side of the endothelium and is an important mediator of vascular permeability. Removal of the ESL has been shown to increase vascular permeability. In addition, the ESL is an important barrier between the endothelium and circulating inflammatory cells such as neutrophils and monocytes (precursors of

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macrophages). Previous studies have demonstrated that ESL degradation increased the adhesion of inflammatory cells to the endothelial surface and increased migration of inflammatory cells to the interstitium\textsuperscript{26-28}.

Considering the crucial regulating role of macrophages in nonosmotic sodium storage and the fact that the ESL affects migration of inflammatory cells from the circulation to the interstitium, the ESL might affect nonosmotic skin sodium storage. An intact ESL may prevent migration of inflammatory cells to the skin, thereby affecting nonosmotic sodium storage. ESL damage, on the other hand, may induce skin sodium accumulation. This hypothesis is supported by studies that have shown skin sodium accumulation in diabetes and dialysis patients, who are also known to have a perturbed ESL\textsuperscript{2, 7, 29, 30}. In this respect, sulodexide may affect non-osmotic skin sodium storage in the skin by restoring the ESL and decreasing vascular permeability. Future studies should determine whether the ESL may affect skin sodium accumulation.

**Future thiazide diuretic therapy**

Finally, we have demonstrated that the current treatment of hypertension may be optimized by switching from thiazide-type diuretics, such as hydrochlorothiazide, to thiazide-like diuretics, such as chlorthalidone\textsuperscript{31}. Currently, 90-95% of the patients receiving a thiazide diuretic are treated with a thiazide-type diuretic\textsuperscript{32}. Our analysis in chapter 9 demonstrated that a switch to thiazide-like diuretics may decrease the incidence of cardiovascular events and heart failure by 12% and 21%, respectively. This significant beneficial effect of thiazide-like diuretics is likely to be caused by a more efficient reduction of 24-hour BP due to the longer elimination half-life of thiazide diuretics compared to thiazide-type diuretics\textsuperscript{33}. In addition, thiazide-like diuretics may decrease platelet aggregation and vascular permeability\textsuperscript{34, 35}. The 12% decrease in cardiovascular events matches the decrease that would be expected from a 4-5 mmHg reduction in 24-hour BP, which was observed in a previous study when switching from hydrochlorothiazide to chlorthalidone\textsuperscript{33, 36}. An additional 4-mmHg BP reduction in subjects that are currently treated with thiazide diuretics may have a significant effect on health care quality and costs.

Large clinical trials have shown that the average annual incidence of cardiovascular events and cardiovascular mortality in hypertensive patients treated with thiazide diuretics is 3.1% and 2.3%, respectively\textsuperscript{37-41}. When extrapolating these numbers to the population receiving thiazide diuretics in the Netherlands (1 million subjects), this would account for approximately 31,000 cardiovascular events and 23,000 deaths annually\textsuperscript{32}.

In 2011, the health care costs of cardiovascular diseases in the Netherlands were 8.3 billion euros\textsuperscript{42}. A new event of myocardial infarction leads to approximately €15,000 of direct health care costs in the first year following the event\textsuperscript{43}. Stroke and heart failure have been estimated to cost €26,600 and €1,550 in the first year after the event\textsuperscript{43}. Using the data that is shown above, we calculated that the decrease in cardiovascular events that is expected from an
additional 4 mmHg BP decrease, in the population of patients receiving thiazide diuretics in the Netherlands, would reduce direct health care costs by approximately 66 million euros in the first year if the more effective strategy was implemented in 85% of all cases. In subsequent years, the reduction in health care costs will be even larger as new cases of cardiovascular events will develop and patients that have developed a cardiovascular event will continue to generate health care costs. As a result, the cumulative savings over a 4-year period that can be expected from a 4 mmHg decrease of BP may be around 557 million euros. These analyses are based on direct health care costs and do not include indirect costs as a result of loss of productivity, informal care and benefit payments that will be at least as large as costs that are due to direct medical costs.

Thiazide diuretics are among the cheapest antihypertensive drugs available. In the Netherlands, the annual costs of hydrochlorothiazide, 25 and 50 mg, are 5.15€ and 15.35€, respectively. Chlorthalidone, 12.5 mg and 25 mg, costs 23.99€ and 7.87€ each year, respectively.

The current indirect evidence indicates superiority of thiazide-like diuretics. Because there are no direct comparisons between thiazide-type and thiazide-like diuretics that have investigated cardiovascular outcome, most guideline committees, with exception of the National Institute for Health and Care Excellence (NICE) guideline, do not distinguish between both diuretic groups for antihypertensive therapy. The need for a direct comparison between thiazide-type and thiazide-like diuretics is further illustrated by an upcoming open label, point-of-care trial (Diuretic Comparison Project (DCP)) in the United States, which will randomize 13,500 hydrochlorothiazide users to hydrochlorothiazide or chlorthalidone to compare the incidence of cardiovascular events during a three-year follow-up.

In conclusion, this thesis demonstrates that sodium homeostasis is more complicated than the widely accepted two-compartment model. More research is needed to understand the (patho)physiology of nonosmotic sodium storage including the interaction between the ESL and the skin interstitium. Clarification of the exact physiology of sodium homeostasis may improve treatment of dysnatremic patients. Also, this thesis provides new therapeutic options that may improve treatment of patients with hypertension and volume overload in the future.

REFERENCES


increased in EXT1-2 +/- mice. Together, these data demonstrate that heparan sulfate polymerization had abnormal sodium and water homeostasis. Relative to wildtypes, EXT1-2 +/- mice had a decreased skin sodium and water content, higher heart rate, decreased whereas no change was observed in wildtypes. Also, we observed an increase in skin that were measured and the changes that were expected according to the Adrogue-Madias and Nguyen-Kurtz formula. These formulas are widely implemented in the clinical setting to predict changes in plasma sodium concentration following infusion therapy in dysnatremic patients. However, both formulas are based on the classical two-compartment model and do not take into account non-osmotic sodium storage in the skin or ESL. Considering the volume of the skin interstitium and ESL, non-osmotic sodium storage may have less capacity for non-osmotic sodium storage.

We examined whether the observed changes of plasma sodium concentration correlates with ESL thickness in healthy volunteers. We observed significant differences between changes in plasma sodium concentration and the estimated ESL thickness in healthy volunteers. Furthermore, we observed that mice with defective heparan sulfates and heterozygous loss of these genes has been shown to result in shorter ESL thickness. As a result, these mice of EXT1 and EXT2 (EXT1-2 +/-) had an 80% reduction in ESL thickness. As a result, these mice may have less capacity for non-osmotic sodium storage. We observed that mice with defective heparan sulfate polymerization had abnormal sodium and water homeostasis. Relative to wildtypes, EXT1-2 +/- mice had a decreased skin sodium and water content, higher heart rate, and may be able to prevent sodium induced volume expansion. Acute hypertonic NaCl infusion did result in a depletion. In addition, EXT1-2 +/- mice had endothelial dysfunction. After high sodium intake, skin sodium and water content of EXT1-2 +/- mice increased significantly and heart rate increased in EXT1-2 +/- mice. Together, these data demonstrate that heparan sulfate polymerization had abnormal sodium and water homeostasis. Relative to wildtypes, EXT1-2 +/- mice had a decreased skin sodium and water content, higher heart rate, whereas no change was observed in wildtypes.

High sodium intake results in salt-sensitive hypertension in rats. A summary of the current understanding of the mechanisms underlying hypertension in individuals with elevated plasma sodium concentration is presented. In this context, the role of heparan sulfate chains is discussed, as these compounds have been shown to have various physiological functions and may be involved in the regulation of blood pressure. The importance of these findings for the development of therapeutic strategies targeting endothelial functions, and may be able to prevent sodium induced volume expansion. Acute hypertonic NaCl infusion did result in a depletion. In addition, EXT1-2 +/- mice had endothelial dysfunction. After high sodium intake, skin sodium and water content of EXT1-2 +/- mice increased significantly and heart rate increased in EXT1-2 +/- mice. Together, these data demonstrate that heparan sulfate polymerization had abnormal sodium and water homeostasis. Relative to wildtypes, EXT1-2 +/- mice had a decreased skin sodium and water content, higher heart rate. Also, we observed an increase in skin that were measured and the changes that were expected according to the Adrogue-Madias and Nguyen-Kurtz formula. These formulas are widely implemented in the clinical setting to predict changes in plasma sodium concentration following infusion therapy in dysnatremic patients. However, both formulas are based on the classical two-compartment model and do not take into account non-osmotic sodium storage in the skin or ESL. Considering the volume of the skin interstitium and ESL, non-osmotic sodium storage may have less capacity for non-osmotic sodium storage.

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43. CBO. Multidisciplinaire Richtlijn Cardiovascular Risicomanagement. 2011.


