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Vasopressin in chronic kidney disease, in particular ADPKD
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Introduction and aims of this thesis
Introduction
This thesis investigates the role of vasopressin in chronic kidney disease and in particular in autosomal dominant polycystic kidney disease (ADPKD). This chapter focuses on the role of vasopressin in physiology and pathophysiology. In Chapter 2 more extensive information is provided on the pathophysiology, clinical symptoms and possible future treatment options of ADPKD.

Vasopressin and the urine concentrating capacity of the kidney
Arginine vasopressin, also called anti-diuretic hormone, plays an important role in the urine concentrating capacity of the kidney. This complex mechanism that generates urine that is markedly more concentrated than the other body fluids is one of the more spectacular functions of the body. The capacity of the kidneys to deliver a urine osmolality that varies widely in response to water intake is unique and essential for survival of mammals. In humans urine osmolality can increase up to 1200 mOsm/kg upon water deprivation, equivalent to 4-times the plasma osmolality. After intake of large quantities of water, urine osmolality may decrease to 50 mOsm/kg, about 6 times lower than plasma osmolality.\textsuperscript{1} Although this variability in urine osmolality may seem impressive, in comparison to other species we are only mediocre performers. For instance, camels can concentrate to 1800 mOsm/kg and domestic cats can concentrate urine to above 3000 mOsm/kg.\textsuperscript{2} The highest urine concentrating capacity is seen in rodents. The spinifex hopping mouse (\textit{Notomys alexis}) deserves the title of ‘urine concentrating champion’ with reported values of urine osmolality above 9000 mOsm/kg.\textsuperscript{3,4}

Mechanisms involving urine concentration
The glomerulus filters around 100 ml plasma per minute, equivalent to 144 liters per 24 hour. The proximal tubule reabsorbs the bulk of water and solutes via isosmotic transport, independent of hydration status.\textsuperscript{5} In order to dilute or concentrate urine, (whatever is necessary depends on water intake and demand of the body) the loop of Henle as well as the collecting duct are important players. As of today the mechanism resulting in concentrated urine is not clearly understood. Three components have been identified so far that are of importance. First, maintenance of a hypertonic medullary interstitium is needed to absorb water out of the lumen of the thin descending limb of the loop of Henle and of the collecting duct. This hypertonicity is mostly maintained by sodium-chloride and urea transport into the interstitium from the ascending limb of the loop of Henle and the collecting ducts, respectively.\textsuperscript{6} Second, a structurally intact countercurrent multiplier system is necessary to establish large osmolality differences along the cortico-medullary axis inside the loop of Henle. This mechanism relies on a water-impermeable barrier that separates descending and ascending parts of the loop of Henle. Active transport of solutes from the ascending to descending side results into a
cortico-medullary osmolality gradient generating large differences of osmolality along the flow direction of the loop of Henle. Figure 1 displays water and salt reabsorption in the proximal tubule and the countercurrent multiplier system in the loop of Henle. Although both aforementioned components deserve attention, as they are complex and examples of the ingenious physiology of the kidney, this thesis focuses on the third component that is essential for urine concentration: regulation of permeability of the collecting ducts for water by arginine vasopressin.

The role of vasopressin in the concentration of urine
Vasopressin is released by the pituitary gland upon an increase in plasma osmolality or decrease in blood volume and blood pressure. The entire collecting duct of the kidney becomes highly permeable for water when vasopressin stimulates vasopressin V2 receptors (V2R) at the basolateral membrane of these cells. Stimulation of these receptors leads to conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) and subsequent activation of protein kinase A. In turn, migration of aquaporin-2 water channels to the apical cell membrane facilitates passive water absorption across the collecting duct. Consequently, urine osmolality increases and plasma osmolality decreases, leading to restoration of the water balance. In Figure 2, the regulation of water reabsorption in the collecting duct by vasopressin is depicted.
Diabetes insipidus

Fluid that is delivered to the distal tubule is hypotonic. When no reabsorption of water in the collecting duct occurs, this fluid remains hypotonic during passage through the collecting duct, despite the large osmotic gradient favoring water reabsorption. When deficient vasopressin action hinders collecting duct water reabsorption, a condition called diabetes insipidus ensues that is characterized by passing large volumes of dilute urine and an increased sense of thirst.

Diabetes insipidus can have both a central or renal origin. Patients with a central diabetes insipidus have a deficiency in secretion of vasopressin from the pituitary gland, whereas a renal origin results from unresponsiveness of the kidney to vasopressin. Therefore, in central diabetes insipidus vasopressin levels are low, whereas in renal (i.e., nephrogenic) diabetes insipidus vasopressin levels are high due to a negative feedback mechanism. Possible causes of nephrogenic diabetes insipidus are amongst others genetic mutations in the V2-receptor or the aquaporin-2 water channel, drug induced (lithium), electrolyte imbalance (hypokalemia or hypercalcemia) or kidney damage due to various renal diseases. The most well-known renal disease which causes diabetes insipidus is autosomal dominant polycystic kidney disease (ADPKD). The exact mechanism by which ADPD causes diabetes insipidus is not yet known, and this thesis tries to increase current knowledge on this mechanism.
**Vasopressin in chronic kidney disease**

Besides its important physiological function in water homeostasis, already in the eighties detrimental renal effects have been described for vasopressin as well. It has been suggested that vasopressin influences the microcirculation of the kidney and thereby induces hyperfiltration.\textsuperscript{16,17} Infusion of vasopressin or dDAVP, a selective V2 receptor agonist, has indeed been found to induce an increase in renal blood flow, glomerular filtration rate (GFR) and protein leakage.\textsuperscript{18-20} A mediator in these vasopressin driven effects on the kidney may be the renin-angiotensin system (RAS), activated directly via the vasopressin V1 receptor (V1R) at the macula densa and indirectly via V2R induced tubuloglomerular feedback.\textsuperscript{21-24} In addition, stimulation of the V1R by vasopressin constricts the efferent arteriole, leading to a further increase in intraglomerular capillary pressure.\textsuperscript{18} Another damaging effect of vasopressin on the kidney may be by stimulation of proliferation and hypertrophy of mesangial cells via the V1 receptor.\textsuperscript{25-28}

**Vasopressin in ADPKD in particular**

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by progressive cyst formation in both kidneys that leads to end-stage renal failure. Vasopressin is assumed to play a detrimental role in the pathogenesis of ADPKD. As described previously, vasopressin stimulates the conversion of ATP into cAMP at the basolateral side of the collecting ducts of the kidney. cAMP is needed to facilitate migration of aquaporine-2 channels into the apical cell membrane in order to reabsorb water. In ADPKD, cAMP also stimulates proliferation of tubular cells and chloride driven fluid secretion into cysts, leading to cyst growth and consequently disease progression.\textsuperscript{29} In Chapter 2 a more extensive overview of ADPKD is given including the role of vasopressin in the pathophysiology of this disease.

**Blockade of vasopressin in ADPKD**

Currently, in 2016, no therapeutic options are available for ADPKD patients to attenuate disease progression. However, research dedicated to ADPKD has intensified in the last decade. Several studies investigated blockade of the V2R as possible treatment option. Blocking the V2R in animal models for polycystic kidney disease delayed disease progression.\textsuperscript{30-35} These promising results led to human intervention studies. A recent multicenter randomized controlled trial showed that the vasopressin V2 receptor antagonist tolvaptan slowed the increase in total kidney volume and the decline in kidney function over a 3 year period in patients with relatively early stage ADPKD.\textsuperscript{36} The most frequently reported adverse events were polyuria and polydipsia. These adverse events can be expected as water reabsorption in the collecting duct relies on stimulation of the V2R. The beneficial renoprotective effect of vasopressin V2 receptor antagonist treatment is therefore accompanied by a strong aquaretic response. As a result of the positive outcome of the clinical trial, tolvaptan the vasopressin V2 receptor
antagonist has been granted marketing authorization for patients with ADPKD by among others the European Medicines Agency. Optimum timing of treatment start and dosage of the drug are yet debated as all studies investigated a fixed dose treatment regimen in relatively early stage of disease. It has been suggested that disease severity and treatment duration may influence treatment efficacy, as indicated by a decline in aquaretic response to V2 receptor antagonism in later stage disease and during prolonged treatment. This thesis aims to further investigate these issues.

**Copeptin as marker for vasopressin**

The assay for vasopressin is laborious and needs to be conducted by an experienced analyst. Moreover, vasopressin is assumed to have limited ex-vivo stability, making measurement in samples that have been stored for prolonged periods of time unreliable. Epidemiological studies are therefore challenging. Copeptin is increasingly used as surrogate marker for vasopressin. Copeptin, a 39-aminoacid glycopeptide, is part of the vasopressin precursor, pre-pro-vasopressin. When this precursor is split, copeptin and vasopressin are produced in equimolar amounts. In Figure 3, a schematic representation of the vasopressin precursor peptide is given. It has been demonstrated that copeptin levels correlate well with vasopressin levels during physiological changes in plasma osmolality, from water excess to dehydration, and also in pathologic states, for example in septic shock. Measurement of copeptin is performed with a semi-automatic analyzer (Kryptor analyser, ThermoFisher, Henningsdorf/Berlin) and takes only a few hours. Given this relative easy method of measurement, together with the assumed stable ex-vivo characteristics, copeptin is a promising surrogate marker for vasopressin that may facilitate epidemiological studies. However, whether copeptin is a reliable marker in patients with impaired kidney function needs to be investigated as the metabolic fate of copeptin is not known, and copeptin could be cleared by the kidney, another topic that is addressed in this thesis.

**Figure 3:** Schematic representation of the vasopressin precursor peptide, preprovasopressin. The numbers indicate amino acids of the human protein. Figure derived from Morgenthaler et al.
Aims of this thesis

In this thesis vasopressin and its precursor copeptin are studied in chronic kidney disease, and in particular in ADPKD. The central aim is to study to what extent vasopressin levels are elevated in chronic kidney disease and in ADPKD, and whether elevated vasopressin levels are a causal factor in disease progression.

Part 1 investigates whether plasma copeptin is a reliable marker for plasma vasopressin, also in patients with chronic kidney disease. Chapter 3 compares the ex-vivo stability of copeptin and vasopressin and studies whether various sample handling and storage conditions influence copeptin and vasopressin concentration. Chapter 4 and 5 focuses on the effect of renal clearance on copeptin to determine whether copeptin is a suitable marker for vasopressin in patients with impaired kidney function. In Chapter 4 copeptin levels in healthy kidney donors before and after donation are studied. Because the remaining kidney after donation is without damage, it is possible to examine specifically the effect of a decrease in glomerular filtration rate on copeptin levels. Chapter 5 investigates the association between renal function and the copeptin/vasopressin ratio in healthy volunteers, chronic kidney disease patients with a wide variety of renal function and patients on dialysis. In case glomerular filtration plays no important role in clearance of copeptin from the body, it is expected that the copeptin/vasopressin ratio is independent of kidney function.

Part 2 focuses on the maximal urine concentrating capacity and vasopressin response during water deprivation in patients with chronic kidney disease. In Chapter 6 ADPKD patients in early stage disease with normal eGFR and healthy volunteers matched for age, sex and renal function participated in a water deprivation test. This study examines whether ADPKD patients have an impaired concentrating capacity and consequently elevated vasopressin levels already in early stage of their disease. In Chapter 7 similar water deprivation tests were performed in ADPKD patients, but this time patients with an impaired kidney function were included. IgA nephropathy patients, matched for kidney function, age and sex, were chosen as control group to compare the concentrating capacity and vasopressin response in patients with predominantly interstitial damage (ADPKD) to patients who have mostly glomerular dysfunction (IgA nephropathy).

Part 3 examines vasopressin as potential causal factor in kidney disease progression. Chapter 8 examines the association between plasma copeptin and disease severity and progression in IgA nephropathy patients during 5 year follow up. Furthermore, it is studied whether copeptin adds prognostic value over established IgA nephropathy risk markers. Chapter 9 aims to investigate prospectively the association between copeptin and prognosis with respect to kidney function in subjects with ADPKD.
In Chapter 10 optimal timing of start and optimal dosage of vasopressin V2 receptor antagonist treatment in ADPKD is studied. Possibly disease severity and treatment duration interfere with treatment efficacy, as suggested in a previous study by a decline in aquaretic response to V2 receptor antagonist treatment in later stage disease and during prolonged treatment. Therefore, it is investigated whether the renoprotective effect of the V2 receptor antagonist can be optimized when the dose of the V2 receptor antagonist is increased during treatment that is started at an early and later stage of the disease. For this study a Pkd1-deletion mouse model was used. Chapter 11 explores the ability of urine osmolality and plasma osmolality as marker for vasopressin activity in ADPKD patients. The associations between plasma and urine osmolality and copeptin is investigated and it is tested whether these associations are influenced by disease severity. Furthermore, the associations of urine and plasma osmolality as well as plasma copeptin concentration with the rate of renal function decline during follow-up are investigated. In Chapter 12, the results of the previous chapters are summarized and placed into context. In addition, the implications of the findings in this thesis and future perspectives are discussed.
References


INTRODUCTION AND AIDS OF THIS THESIS

1

introduction and aims of this thesis