Vasopressine : une nouvelle cible pour la prévention ou le traitement de certaines maladies rénales ?

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Lise BANKIR: No Conflict of Interest
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Outline

Introduction about vasopressin (VP) and its receptors

Adverse effects of VP through V2 receptors

- Polycystic kidney disease
- Chronic kidney disease
- Albuminuria, diabetic nephropathy
- Hypertension

Adverse effects of VP through V1 receptors

- Glycemia, metabolic syndrome

Perspectives
Vasopressin = AVP or Antidiuretic hormone = ADH

- Small peptidic hormone (9 amino acids), very ancient in evolution
- Synthetized in the hypothalamus, stored in the neurohypophysis
- Released under the influence of two different stimuli
  - ↑ plasma osmolality (mainly **natremia**) or ↓ blood volume
- Allows the production of hyperosmotic urine
  *(no other hormone can replace it; lack of AVP = diabetes insipidus)*
AVP receptors: The classical view

V2 \( (cAMP) \)

\[
\downarrow
\]

Renal Collecting Duct

AQP2: \( \rightarrow \) Permeability to water

\( \rightarrow \) Water Conservation

V1a \( (Ca^{++}) \)

\[
\downarrow
\]

Vasc. smooth muscle cells

\( \rightarrow \) Vasoconstriction

\( \rightarrow \) Blood pressure

V1b \( (Ca^{++}) \)

Expressed in multiple organs. In vivo effects poorly known
### AVP receptors: Multiple target tissues

<table>
<thead>
<tr>
<th></th>
<th>V2R (cAMP)</th>
<th>V1aR (Ca ++)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney</strong></td>
<td><strong>COLL. DUCT (BASOLATERAL)</strong></td>
<td>Glomeruli &amp; Macula Densa</td>
</tr>
<tr>
<td></td>
<td>Coll. Duct (primary cilium)</td>
<td><strong>Coll. Duct (luminal)</strong></td>
</tr>
<tr>
<td></td>
<td>Thick ascending limb</td>
<td>Interstitial cells of the medulla</td>
</tr>
<tr>
<td>Blood vessels &amp; blood</td>
<td><strong>Endothelium (NO)</strong></td>
<td><strong>SMOOTH MUSCLE CELLS</strong></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td>Platelets</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td><strong>Type II pneumocytes</strong></td>
<td><strong>HEPATOCYTES</strong></td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td><strong>Inner ear, Eye (?)</strong></td>
<td>Certain brain nuclei</td>
</tr>
<tr>
<td>Other organs</td>
<td></td>
<td>Adrenal glands</td>
</tr>
</tbody>
</table>

**V1bR:** **Alpha and Beta cells of pancreatic islets**, Adrenals, Kidney Coll. Duct, Spleen, Uterus, Breast, Thymus, Heart
Low interest in Vasopressin for several decades

In contrast to the renin-angiotensin-aldosterone system, Vasopressin has been poorly studied in the last 3-4 decades (except for its acute effects on responsive tissues)

WHY?

✓ Very low concentration (from undetectable to 3 pmol/L \(10^{-12}\)M)
✓ Difficult and time consuming immuno assay. Lower limit = 0.5 pmol/L
✓ No good antagonists for a long time
✓ Not much attention paid by physicians to urine volume
✓ Urine osmolality rarely measured routinely

New interest in the last few years:

- Selective, orally active receptor antagonists are now available = VAPTANS
- Immuno-assay for COPEPTIN developed by B.R.A.H.M.S. / ThermoFisher
Copeptin, a surrogate marker of vasopressin

Pre-pro-hormone of vasopressin

The 3 peptides are released simultaneously in the blood in equimolar amounts

Compared to vasopressin, copeptin:

- Has a longer biological half-life ⟷ Higher levels in the blood
- Has a higher molecular weight ⟷ Easier to make antibodies
- Is more stable in vitro over time

Immuno-assay developed by B.R.A.H.M.S., (now ThermoFisher)
Sex differences in urine osmolality and in plasma copeptin concentration in normal subjects

Urine osmolality

Plasma copeptin concentration

This sex difference may explain the greater susceptibility of males to nephrolithiasis, hypertension, more rapid progression of CKD, etc....
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- Glycemia, metabolic syndrome

Perspectives
Effect of Vasopressin in ADPKD

The initial impairment in renal function is due to a genetic defect

- Then, well demonstrated: cAMP promotes renal cyst growth.

- Hypothesis: Because vasopressin induces cAMP formation, via V2 receptors, it should participate to the enlargement of cysts and thus accelerate the progression of the disease.
Vasopressin and PKD: Brattleboro rats x PCK rats

Rats with a genetic defect leading to PKD do not develop cysts if they have no vasopressin. dDAVP infusion results in cyst development.

**TEMPO trial: Vasopressin V2R antagonist in ADPKD**

Randomized, Placebo-Controlled, Parallel Assignment, Double Blind, Safety/Efficacy Study.

1500 ADPKD subjects with still good renal function. Duration: 3 years

Risk of worsening kidney function

Risk of clinically significant kidney pain

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*Torres V et al, NEJM, 2012*
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Perspectives
Association of copeptin with accelerated renal function decline in renal transplant recipient (n = 548)

Remains significant after adjustment for age, gender, initial GFR and other confounding factors

Meijer et al... Gansevoort, Transplantation 2010
Association between 24 h urine volume and renal function decline in a general population

Cohort of 2148 subjects of a Canadian population with 5.7 year follow up

Significant (p < 0.02) after adjustment for:
- age, gender,
- baseline estimated GFR,
- dipstick protein,
- medication for hypertension (including diuretics),
- diabetes
- cardiovascular disease.

Urine Osmolarity and Risk of Dialysis Initiation in a Chronic Kidney Disease Cohort – a Possible Titration Target?

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Plos One, March 2014, 9(3), e93226
Objective and Design

**Objective**: Look for possible association between urine osmolarity and/or urine volume and the progression of CKD

**Primary endpoint**: Time to dialysis (with death as a competing risk)

**Design**: Retrospective cohort analysis of patients with chronic kidney disease stages 1 to 4. Median follow-up: 92 months [76-95]

**Statistics**: Multivariate proportional sub-distribution hazards model for competing risk data (according to Fine and Gray)
Patients

- All patients attending the Nephrology outpatient Department for 3 years (Jan 2000 to Dec 2002) (single-centre cohort study).

- **Baseline value** for each parameter = mean of all measurements during a run-in phase of one year.
  Median: 5 measurements [25th-75th percentiles: 3-8]

- **Inclusion criteria**: Minimum of two visits with 24-h urine collection before and after baseline

- **Exclusion criteria**:
  - Urine volume less than 500 ml/24h
  - Creatinine clearance below 15 ml/min (= CKD 5)

- **Number of patients**: 372 patients examined. **273 were eligible.**
  Mortality data and data on the initiation of dialysis until 31/12/2008 obtained from Austrian registries
Variables, Statistical analysis / Follow-up

Urine osmolarity was estimated according to the following formula: \( U_{\text{osm}} = (U_{\text{Na}} + U_{K}) \times 2 + U_{\text{urea}} \)

Multivariate competing risk regression analysis with death as the competing risk
Adjusted for these variables at baseline:
- Age
- Creatinine clearance
- Proteinuria
- Type of underlying renal disease
- Beta-blocker and/or diuretic therapies

Median follow up 92 months (76 to 95)
End stage kidney disease developed in 105/273 patients (39%)
Cumulative incidence for dialysis initiation according to baseline urine osmolality

Considering the the 10\(^{th}\), 50\(^{th}\) et 90\(^{th}\) percentiles of $U_{\text{osm}}$ corresponding to 315, 510 or 775 mosmol/L, respectively

Cumulative incidence for dialysis initiation according to baseline urine osmolality

Follow up (months)

- Pts with 775 vs 510 mosm/L
  \[ \text{Unadjusted SHR (with death as a competing risk)} = 1.54 \text{ (95\% CI: 1.03 to 2.28)} \]

- Pts with 315 vs 510 mosm/L
  \[ \text{Unadjusted SHR (with death as a competing risk)} = 0.61 \text{ (95\% CI: 0.39 to 0.96)} \]
Among patients with chronic kidney disease, for an equal level of remaining renal function, those with higher urine osmolarity at baseline were more likely to progress to dialysis during subsequent years.
Is there a rationale explaining why and how a high level of vasopressin (copeptin) and/or a low urine flow rate could exert an adverse effect on renal function?

Previous experimental studies in rats support a causal link between vasopressin and progression of kidney disease.

(most of these studies were performed in my laboratory)
Effects of increased water intake in a rat model of chronic kidney disease (5/6 nephrectomy)

Bouby Bankir, Am. J. Physiol. 1990
Interpretation

Why do vasopressin and/or a high urine concentration contribute to kidney disease progression?
Increased GFR with increasing urine concentration

Healthy rats, studied after one week on High Water intake or dDAVP infusion
Inulin clearance based on 24h urine

Bouby et al, JASN, 1996
Increased GFR with increasing urine concentration

Healthy rats, studied after one week on High Water intake or dDAVP infusion
Inulin clearance based on 24h urine

N = 12 healthy subjects, acute study
- High Hydration = 4.0 ml/kg BW/30 min
- Low Hydration = 0.5 ml/kg BW/30 min
  Two weeks apart (random order)

\[ r = 0.798 \]

**Bouby et al, JASN, 1996**

**Anastasio et al, Kidney Int. 2001**
GFR rises with urine concentration **ONLY in when Uosm > Posm**

- Healthy rats, **studied after one week** on High Water intake or dDAVP infusion
  - Inulin clearance based on 24h urine

- N = 12 healthy subjects, **acute study**
  - High Hydration = 4.0 ml/kg BW/30 min
  - Low Hydration = 0.5 ml/kg BW/30 min
  - Two weeks apart (random order)

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**Bouby et al, JASN, 1996**

**Anastasio et al, Kidney Int. 2001**
Vasopressin does not act only on water permeability (AQP2). It also regulates ENaC and Urea Transporters.

Protocol: Urine concentration altered for 1 week in normal rats (dDAVP infusion or addition of water to the food)

Result: Urine osmolality increases at the expense of a reduced efficiency in Na and Urea excretion

Bouby et al, JASN 1996
GFR and urine concentration ... This is a "J" curve

"Hyperfiltration"

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Perspectives
Vasopressin and Diabetes mellitus

- Nephropathy = frequent complication of diabetes (but does not concern all DM patients). *First sign is a rise in albumin excretion*

- Vasopressin is known to be increased in type 1 and type 2 diabetes mellitus, in humans and in rats

- The vasopressin response to different stimuli is exaggerated in diabetes mellitus

--->> DOES VASOPRESSIN CONTRIBUTE TO DIABETIC NEPHROPATHY?
Copeptin (a surrogate marker of vasopressin) is associated with microalbuminuria in a large population cohort (n = 7593).

Abcissa = Increasing quintiles of plasma copeptin concentration

Meijer et al, Kidney Int. 77:29-36, 2010
Renal function decline in diabetic patients

Copeptin measured in 3101 participants with type 2 diabetes and albuminuria, during a 6 year follow-up (DIABHYCAR trial)

The yearly decline in eGFR was 2.5 to 3.0-fold faster in patients of Tertile 3 than in those of Tertile 1.

Velho et al, Diabetes Care 2013
dDAVP infusion increases urinary albumin excretion in healthy subjects (n = 6)

Rise in UAE in DI subjects with mutation of AQP2. NO rise in UAE in DI subjects with mutation of the V2 receptor.
A V2R antagonist protects the kidney in a rat model of type 1 diabetes mellitus (streptozotocin)

In rats with type 1 DM, a selective V2 receptor antagonist was given orally at doses reducing about three fold the spontaneous urine concentration.

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Bardoux ...and Bankir, NDT 2003
Relationship between $C_{\text{creat}}$ or albuminuria and urinary concentrating activity in DM rats

13 non-treated Diabetic-Control rats on Week 9

Bardoux et al, NDT 18:497, 2003
Albuminuria in 13 NON-TREATED diabetic control rats

No difference at the beginning

But different evolution over time in different rats

"Progressors"

"Non progressors"

Bardoux et al, NDT 18:497, 2003
Comparison of DM-Cont Progressors and Non-Progressors (week 9)

Renal mass (left kidney) (g)

Glomerular volume (nl)

Mesangial surface / glomerular surface (%)

Bardoux et al, NDT 18:497, 2003
Vicious circle due to hyperfiltration

Glomerular hyperfiltration

Increased glomerular pressures and flows

Reduced functioning nephron number

Glomerular sclerosis

Increased energy demand for reabsorption of extra solutes filtered

Increased oxidative stress and interstitial inflammation

Primary renal disease

High protein diet or diabetes mellitus

Adapted from Brenner, AJP 1985
Vicious circle due to hyperfiltration

High protein diet or diabetes mellitus

AVP

Glomerular hyperfiltration

Increased glomerular pressures and flows

Glomerular sclerosis

Increased energy demand for reabsorption of extra solutes filtered

Increased oxidative stress and interstitial inflammation

Reduced functioning nephron number

Primary renal disease

Adapted from Brenner, AJP 1985
Summary: CKD, albuminuria and diabetic nephropathy

- In humans, copeptin (vasopressin) or a high urine osmolarity are positively related to the rate of decline in renal function and to the magnitude of albuminuria.

- Vasopressin increases GFR and urine albumin excretion in healthy rats and humans.

- Vasopressin contributes to progression of CKD and to the albuminuria of diabetic nephropathy in rats.

- Increased water intake or chronic treatment with a V2 antagonist is beneficial in animal models of CKD or diabetes mellitus.

- Inter-individual differences in the susceptibility to diabetic nephropathy (in rats) are related to the intensity of urine concentrating activity.
"Osmotic work"

More than 60 years ago, Thomas Addis recognized that the excretion of toxic wastes (in a concentrated urine) represented ‘osmotic work’ for the kidney when he wrote “the treatment of glomerulonephritis is only a particular application of the general thesis that the major events in the kidney are determined by the amount of ‘osmotic work’ it is called on to do.”

When he recommended his patients with CKD to eat a diet low in protein, Thomas Addis intended "to put their kidneys at rest of osmotic work"

This can also be achieved by increasing fluid intake or antagonizing the V2 effects of vasopressin.
## Two possible strategies to reduce vasopressin's actions

<table>
<thead>
<tr>
<th></th>
<th>Voluntary increase in water intake</th>
<th>Treatment with a V2R antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behaviour</td>
<td>Increase in water intake</td>
<td>Take a drug</td>
</tr>
<tr>
<td>Cost</td>
<td>Nil</td>
<td>High</td>
</tr>
<tr>
<td>Observance</td>
<td>Difficult to drink when not thirsty</td>
<td>Easy. Good observance</td>
</tr>
<tr>
<td>Plasma Osmolarity</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>AVP secretion and Plasma AVP</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Effects mediated by other receptors (V1aR &amp; V1bR)</td>
<td>Low or absent</td>
<td>Increased</td>
</tr>
<tr>
<td>Possible side effects</td>
<td></td>
<td>Increase in heptatic enzymes</td>
</tr>
</tbody>
</table>

(1) Note: The effects mediated by V1a receptors may not be detrimental
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- Glycemia, metabolic syndrome

Perspectives
See these two reviews

**Bankir L, Bichet DG, Bouby N.**
Vasopressin V2 receptors, ENaC, and sodium reabsorption: a risk factor for hypertension?


**Bankir, Bouby and Ritz**
Vasopressin: a novel target for the prevention and retardation of kidney disease?

*Nature Reviews Nephrology*, 2013
Our ancestral heritage

In prehistorical times, the need to conserve water was a strong PRIORITY. Severe lack of water is lethal in a few days. Life expectancy was short. The delayed consequences of high urine concentration did not have time to appear.

In present times, the need to conserve water has decreased because water is easily available (in Western countries).

........... But the mechanisms (and the structure of the kidney) allowing water conservation have remained powerful.

The water conservation mechanisms operate at the expense of a lesser ability to excrete urea, sodium, and other solutes. It induces a glomerular hyperfiltration and a rise in blood pressure. This may have adverse consequences on the long term.
Take-home messages

- More attention should be given to vasopressin (or copeptin) levels and/or urine volume and concentration in human studies.

- Voluntary increase in fluid intake, or treatment with vasopressin V2 antagonists may become new therapeutic strategies for the prevention or retardation of CKD, diabetic nephropathy and some forms of salt-sensitive hypertension.
Thank you for your attention
Rat kidney

Arterial filling