ARGININE VASOPRESSIN (AVP)

AFFECTS BLOOD PRESSURE AND RENAL WATER REABSORPTION

WHAT ELSE DOES IT DO?

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AVP AND THE HYPOTHALAMO-PITUITARY SYSTEM

Koshimizu T et al. Physiol Rev 2012;92:1813-1864
AVP MOLECULE

\[
\text{Cys} \quad \text{Cys} \quad \text{Pro} \quad \text{Gly} \quad \text{Arg} \quad \text{Asn} \quad \text{Gln} \quad \text{Tyr} \quad \text{Phe} \quad \text{NH}_2 \quad \text{NH}_2
\]
AVP (ADH)

- $V_{1a}$ Receptors
  - Regulate Vascular Tone

- $V_2$ Receptors
  - Regulate H$_2$O Reabsorption by the Kidney
Regulation of AVP Secretion

Both increased plasma osmolality and decreased blood volume stimulate AVP secretion, but with different thresholds and sensitivities.

Stricker et al. In: Fundamental Neuroscience. 2nd ed. 2003;1011-1029
Nonpressor and Nonantidiuretic Actions of Vasopressin

Actions of AVP

- Diabetes
- Bone
- Metabolic syndrome
- Pain
- Lipids
- Hypertension
- Chronic Kidney Disease
- HPA Axis
- Hemostasis
- Infection
- Aging
- Social behavior
- Cognition
- Cellular Proliferation
- Inflammation
Arginine Vasopressin Receptors and Their Locations

<table>
<thead>
<tr>
<th>V1a Receptors</th>
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<tbody>
<tr>
<td>Smooth Muscle Cells</td>
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<tr>
<td>Brain</td>
</tr>
<tr>
<td>Adrenal Cortex</td>
</tr>
<tr>
<td>Adipose Tissue</td>
</tr>
<tr>
<td>Hepatocytes</td>
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<tr>
<td>Osteoblasts</td>
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<tr>
<td>Osteoclasts</td>
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</tbody>
</table>
Arginine Vasopressin Receptors and Their Locations Continued..

<table>
<thead>
<tr>
<th>V1b Receptors</th>
<th>V2 Receptors</th>
</tr>
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<tbody>
<tr>
<td>Anterior Pituitary</td>
<td>Basolateral Membrane of Collecting Ducts</td>
</tr>
<tr>
<td>Adrenal Medulla</td>
<td>Alveolar Epithelial Cells</td>
</tr>
<tr>
<td>Islet Cells of Langerhans</td>
<td>Osteoblasts</td>
</tr>
<tr>
<td>White Adipose Tissue</td>
<td>Osteoclasts</td>
</tr>
</tbody>
</table>
AVP AND HEMOSTASIS

- DDAVP increases serum levels of vWF, factor 8 and t-PA via V2 receptors on renal and nonrenal epithelial cells

- Useful for treatment of Von Willebrand’s disease and hemophilia
AVP AND PAIN PERCEPTION

- AVP exerts analgesic actions
- AVP can increase pain threshold when given by intraventricular route (animal study)
- Analgesic actions blocked by V1a receptor antagonist. Intrathecal and intranasal AVP also can reduce pain
AVP AND AGING, SOCIAL BEHAVIOR AND COGNITION

- Klotho increases resistance to oxidative stress (anti-aging), reduces 1,25 Vitamin D (anti-hyperphosphatemia)
- Klotho levels are reduced in dehydrated mice and in studies by high levels of AVP
- AVP increases anxiety (V1a). Neuroleptic drugs decrease AVP levels. Autism linked to mutation in V1a receptor genes.
- Dehydration affects cognitive function and decreases in function are associated with AVP
Ohnishi M et al. FASEB J 24: 3562-3571, 2010
AVP AND BONE

- AVP receptors V1a and V2 on osteoblasts and osteoclasts
- AVP stimulates osteoclasts and inhibits osteoblasts
- Hyponatremia also activates osteoclasts and limits defense against ROS by limiting movement of Vitamin C into cells
Hyponatremia-Induced Osteoporosis

- Animal Study: Hyponatremia produced greater bone loss than aging alone after three months.

- NHANES III: Data revealed hyponatremia was associated with increased odds of osteoporosis at the hip adjusted for age, sex, race, vitamin D25. (OR = 2.85, p<0.01)

AVP AND HYPOTHALAMIC PITUITARY AXIS

- HPA axis involves central CRH and AVP (V1b) responses. V1b is more important in stress situations.

- AVP also acts on receptors in adrenal gland (V1a cortex and V1b medulla) for peripheral stress reactions.
AVP AND INFLAMMATION AND CELL PROLIFERATION

- Inflammatory cytokines such as IL-6 and CRP increase AVP levels (hyponatremia) and AVP via V2 stimulation can reduce inflammation in lungs by local decrease in IL-6.

- Defective response of hypothalamus (CRH and AVP) decreases ACTH and thereby cortisol response which fails to suppress inflammation.

- AVP increases cell proliferation in studies on intestinal epithelial cells, renal mesangial cells (V1a, VEGF) and blockade decreased lung cancer cell growth.
Response to infection involves innate immunity, TLRs, and renal tubular epithelial cells. TLR4 recognizes LPS on gram negative organisms and activates factors which destroy the organism.

DDAVP inhibits LPS induced activation of anti gram negative organism factors. This can be prevented by V2 blockers.

Dehydration and increased AVP may play a role in susceptibility to infection.
AVP AND METABOLIC SYNDROME

Metabolic Syndrome includes:

• Insulin Resistance (DM)
• Dyslipidemia
• Hypertension
• Obesity, Sleep Apnea, Fatty Liver

AVP actions include liver and pancreas effects and ACTH secretion.
AVP AND DIABETIC MELLITUS

- V1a receptors on hepatocytes cause glycolysis and V1b receptors are found on pancreatic alpha cells (glucagon) and beta cells (insulin) but V1b receptors on alpha cells are more sensitive to AVP.

- AVP also stimulates ACTH via V1b receptors in the pituitary and V1a receptors in the adrenal cortex to increase cortisol (glucose).
Cells, Receptors and the Effects of Arginine Vasopressin on the Blood Glucose Levels

<table>
<thead>
<tr>
<th>Cells</th>
<th>Receptors and Effects</th>
</tr>
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<tbody>
<tr>
<td>Hepatocytes</td>
<td>V1a- Glycolysis</td>
</tr>
<tr>
<td>Beta islet cells</td>
<td>V1b- Insulin release</td>
</tr>
<tr>
<td>Alpha islet cells</td>
<td>V1b- Glucagon release</td>
</tr>
<tr>
<td>CNS (Pituitary) cells</td>
<td>V1b- ACTH release increases glucocorticoids</td>
</tr>
<tr>
<td>Adrenal Cortex</td>
<td>V1a- increases glucocorticoids</td>
</tr>
</tbody>
</table>
CRH and AVP cause ACTH to be released from pituitary

stress $\rightarrow$ V1b $\rightarrow$ releases ACTH $\rightarrow$ cortisol $\rightarrow$ glucose

ACTH released by AVP does not respond to negative feedback via cortisol as does CRH induced ACTH release
COPEPTIN AND AVP

- Copeptin surrogate marker of AVP as it is secreted with AVP
- Easier to use as a marker since longer half life, not attached to platelets
- Higher levels correlate with Mets, increased TG levels and predictor of obesity, proteinuria, and DM (15+ years Swedish study)
COPEPTIN AND SERUM OSMOLALITY

Fenske W K et al. JASN 2014;25:2376-2383
AVP AND LIPIDS

- AVP stimulates sympathetic nerve activity in the CNS which can increase fatty acids.
- AVP has an antilipolytic effect involving V1a receptors in adipose tissue. V1a regulates insulin mediated glucose uptake.
- V1a deficient rodents demonstrate increased lipolysis.
- AVP stimulates glycogenolysis in liver increasing glucose and triglyceride levels.
- Blockade of V1b can suppress lipolysis and increase lipogenesis by increasing insulin sensitivity.
AVP AND HYPERTENSION

- AVP deficiency contributes to vasodilation in septic shock
- Studies over last 40 years have cited issues with sodium excretion (less efficient) in black vs white subjects
- Bankir, Parucca and MH Weinberger 2007 published a comprehensive study demonstrating more concentrated urine, higher pulse pressure and delay in sodium excretion in black individuals
Bankir, L et al. CJASN 2: 304-312, 2007
AVP AND CKD PROGRESSION

- Not only previously mentioned actions regarding diabetes mellitus and hypertension but also data relating low urine volumes and CKD progression
- AVP stimulates the renin-angiotensin system via the V2 receptor. May decrease sodium excretion and cause hyperfiltration
- DDAVP infusion increases urine osmolality and increases UAE. AVP infusion increases GFR with increased urine concentration and decreased FENA
- Effects can be altered by ACE and V2 blockade
Bardoux P et al. NDT 18:1755-1763, 2003
IN SUMMARY

- Arginine vasopressin exerts a variety of actions on multiple functions such as pain perception, behavior and cognition.

- Integrity of bone, inflammatory reactions, cell proliferation, and responses to infection and stress are also influenced by AVP.

- Actions of AVP related to metabolic syndrome involving glucose, lipids and blood pressure and effects relating to hydration status, hyperfiltration and proteinuria may influence the progression of chronic kidney disease.
THANK YOU