ARGININE VASOPRESSIN (AVP)

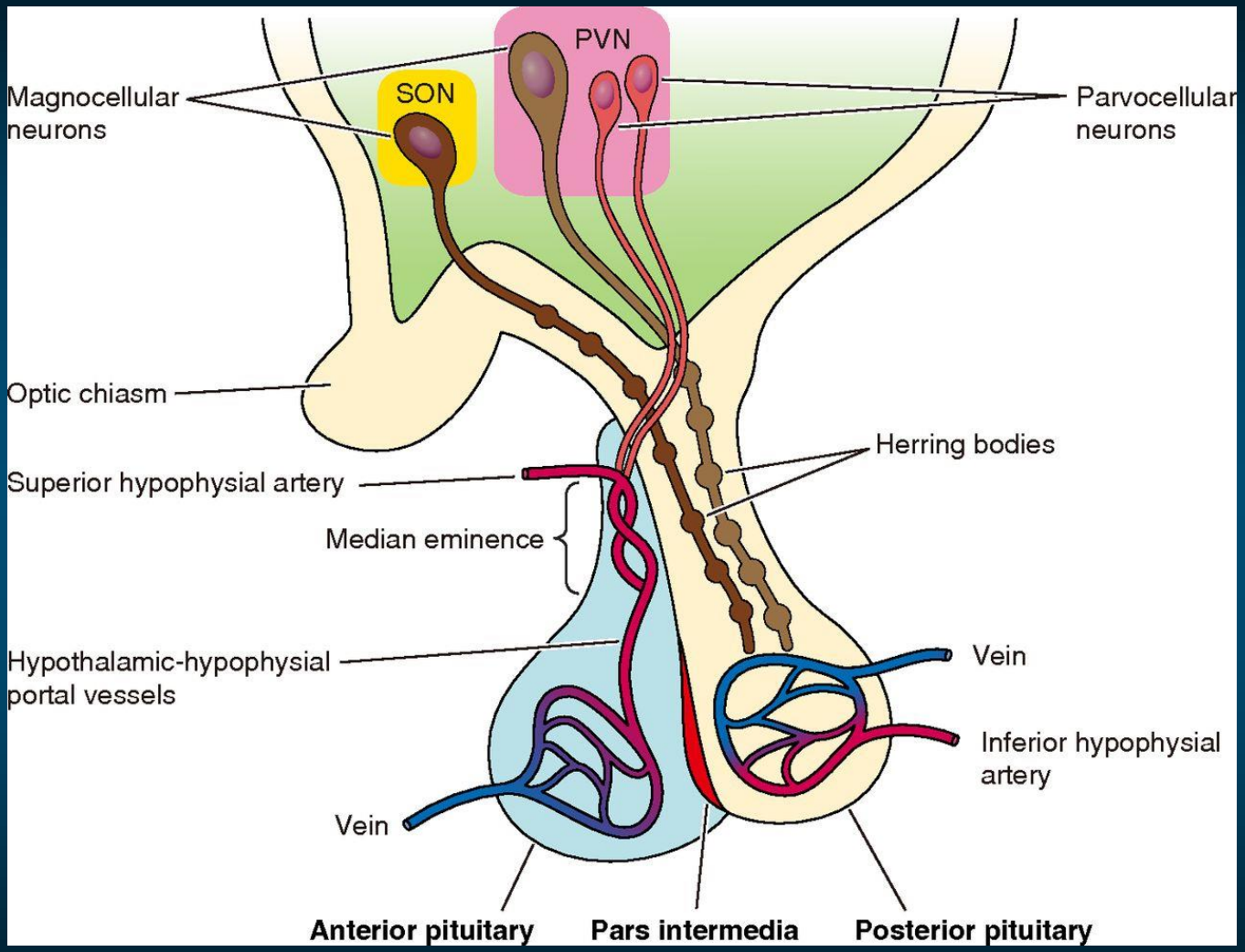
AFFECTS BLOOD PRESSURE AND RENAL WATER REABSORPTION

WHAT ELSE DOES IT DO?

Michael F. Michelis, M.D., F.A.C.P., F.A.S.N.
Director, Division of Nephrology
Lenox Hill Hospital, New York

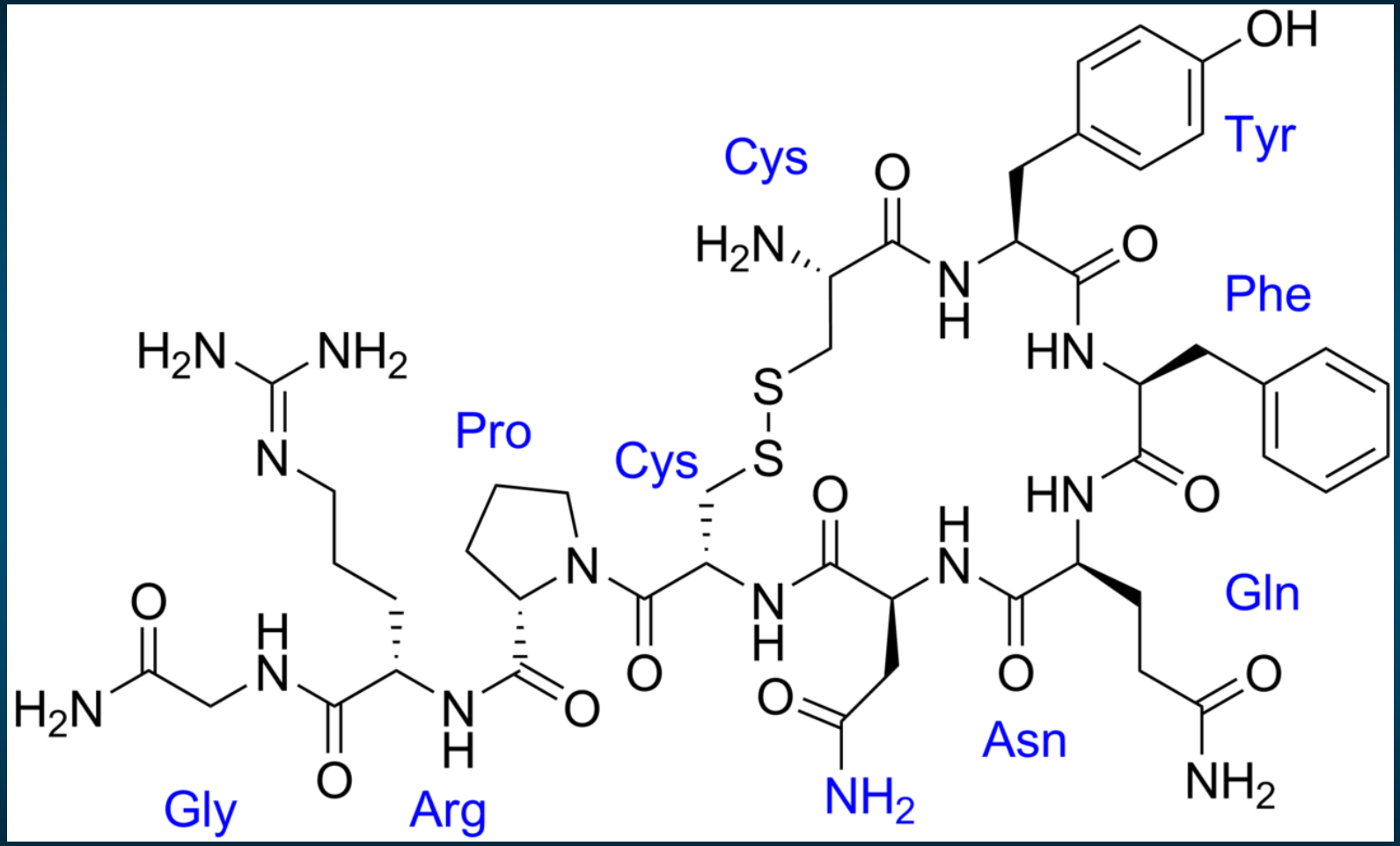
Clinical Professor of Medicine
New York University School of Medicine

AVP AND THE HYPOTHALAMO-PITUITARY SYSTEM

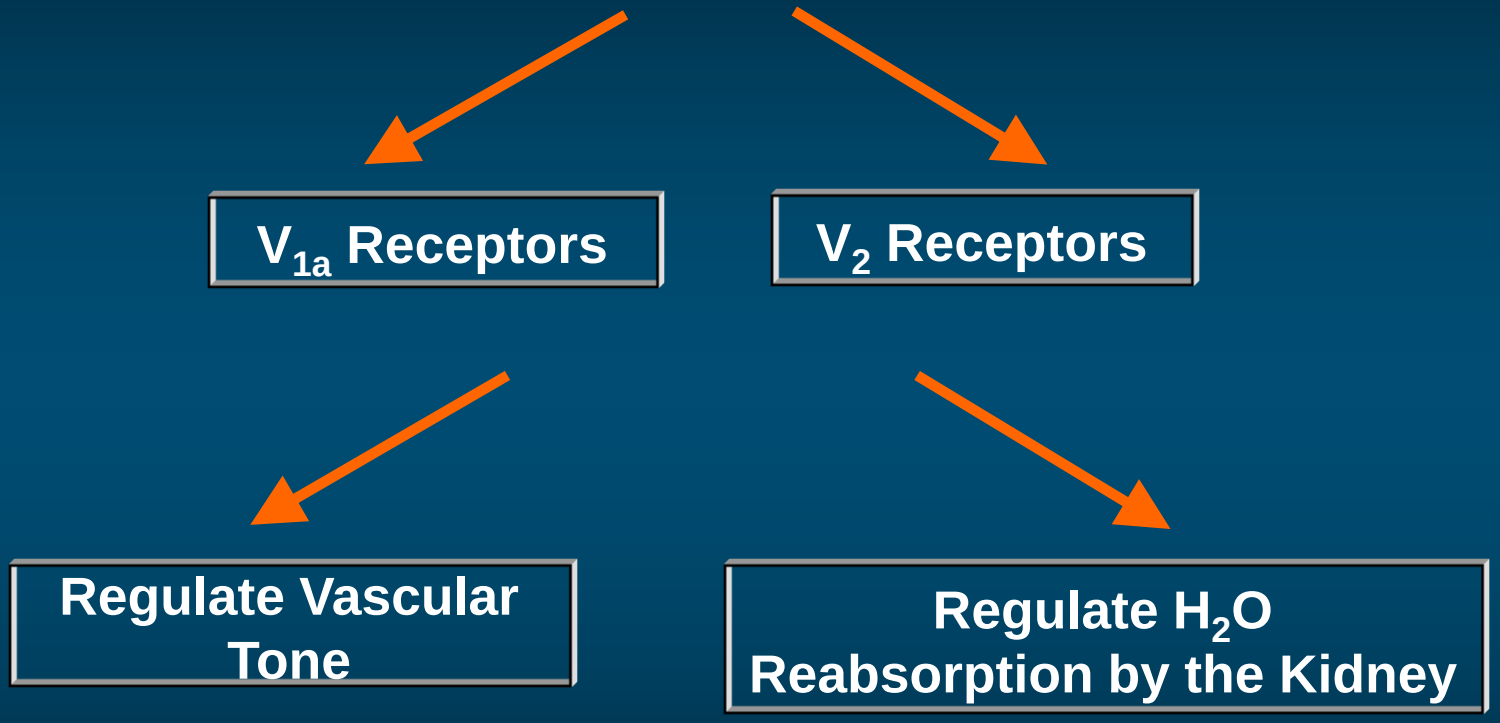


Koshimizu T et al. Physiol Rev 2012;92:1813-1864

AVP MOLECULE

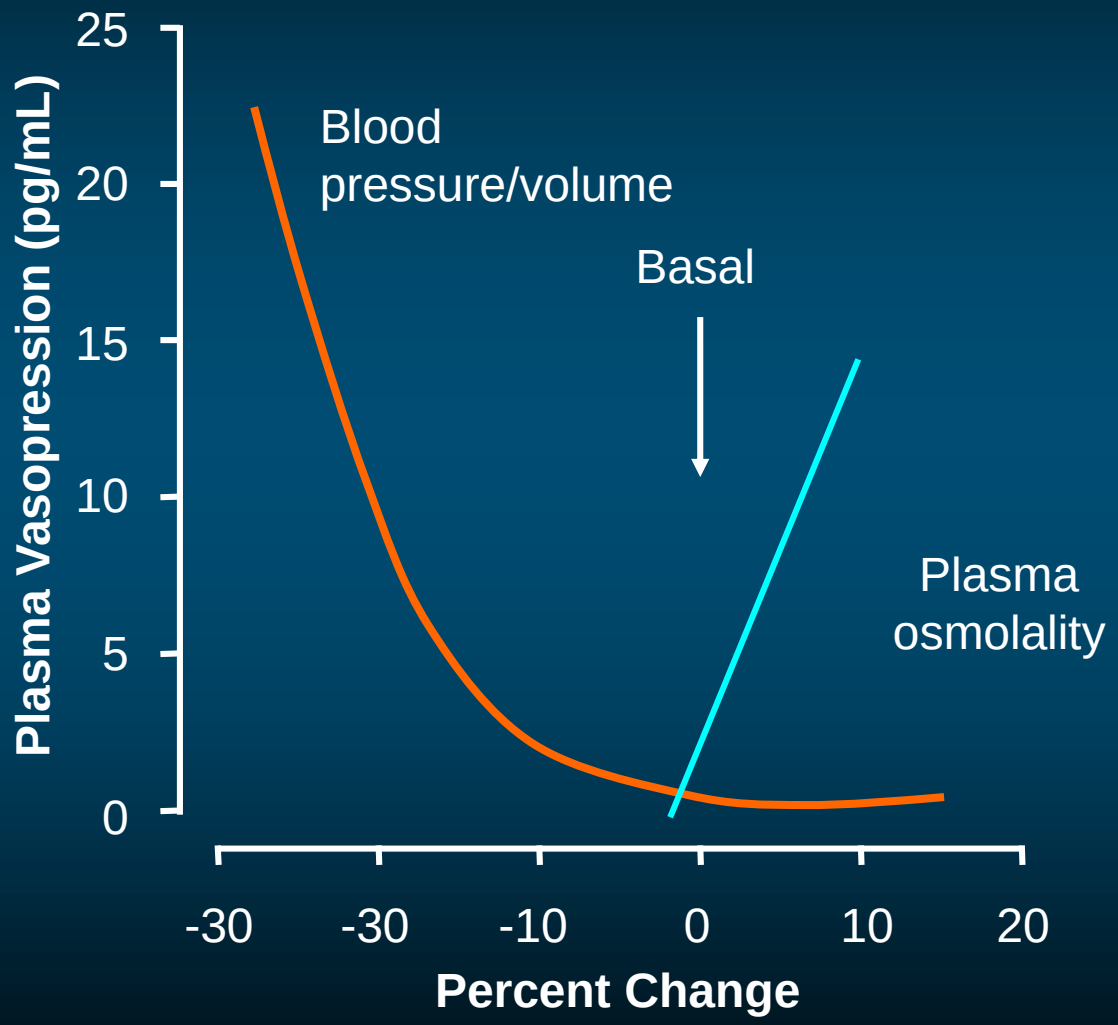


AVP (ADH)


V_{1a} Receptors
V_2 Receptors
Regulate Vascular Tone
Regulate H_2O 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

Arginine Vasopressin Receptors and Their Locations

V1a Receptors
Smooth Muscle Cells
Brain
Adrenal Cortex
Adipose Tissue
Hepatocytes
Osteoblasts
Osteoclasts

Arginine Vasopressin Receptors and Their Locations Continued..

V1b Receptors	V2 Receptors
Anterior Pituitary	Basolateral Membrane of Collecting Ducts
Adrenal Medulla	Alveolar Epithelial Cells
Islet Cells of Langerhans	Osteoblasts
White Adipose Tissue	Osteoclasts

AVP AND HEMOSTASIS

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

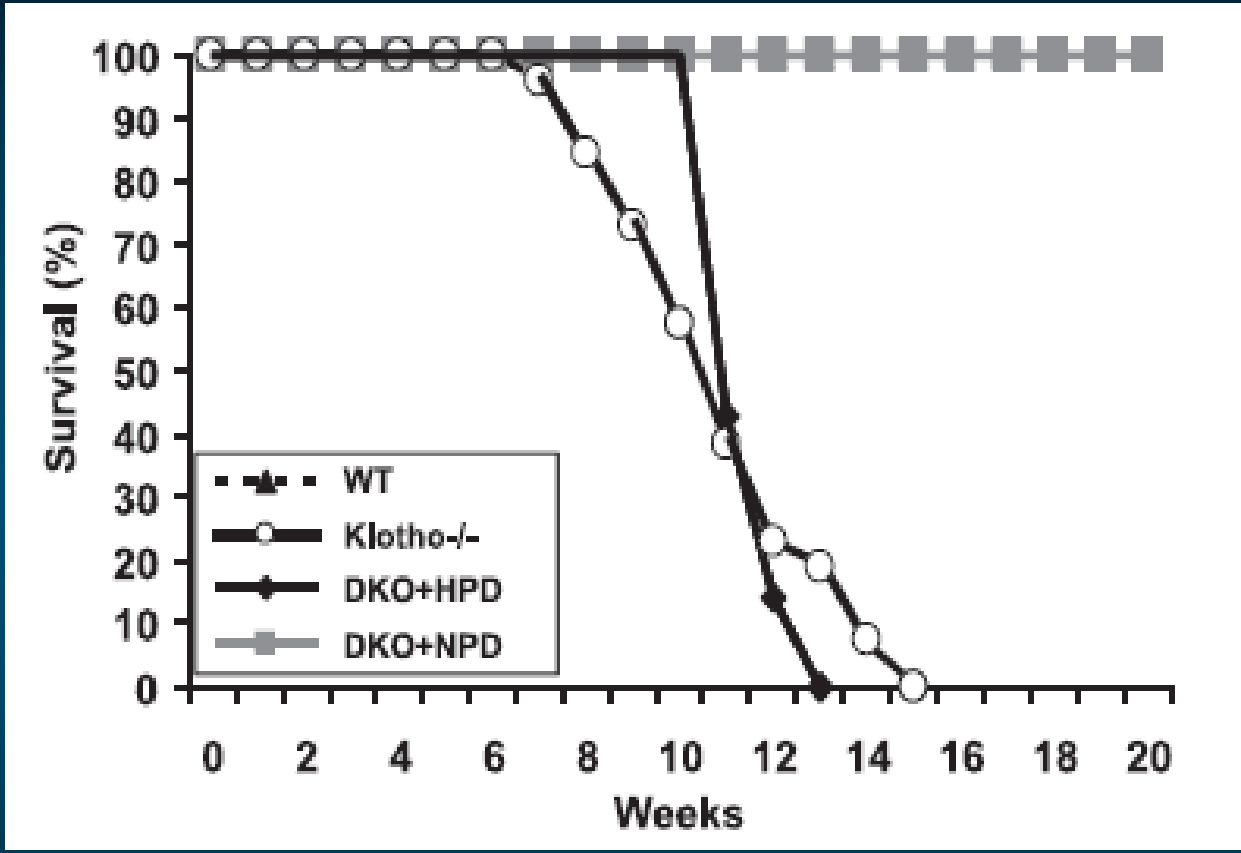
- Useful for treatment of Von Willebrand's disease and hemophilia

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

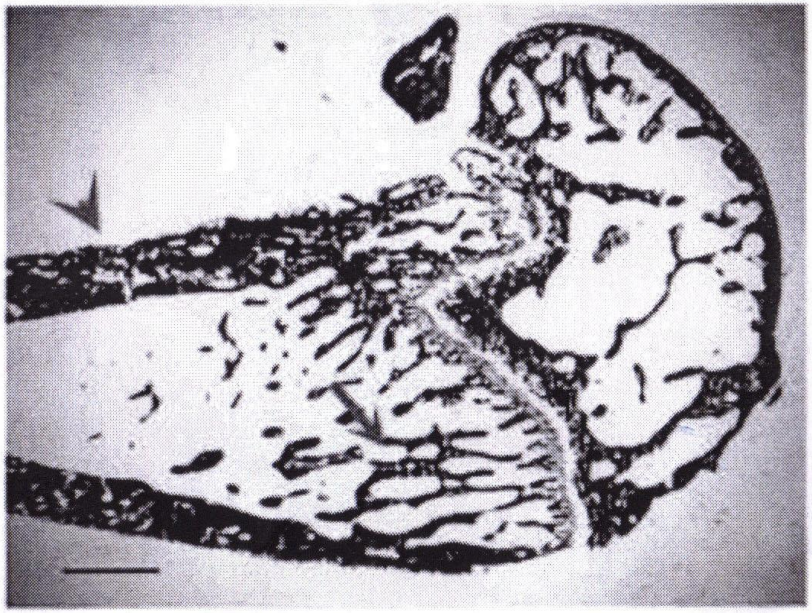
- Animal Study: Hyponatremia produced greater bone loss than aging alone after three months.

- 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, $p<0.01$)

Verbalis JG et al. J Bone Miner Res 25(3): 554-563, 2010

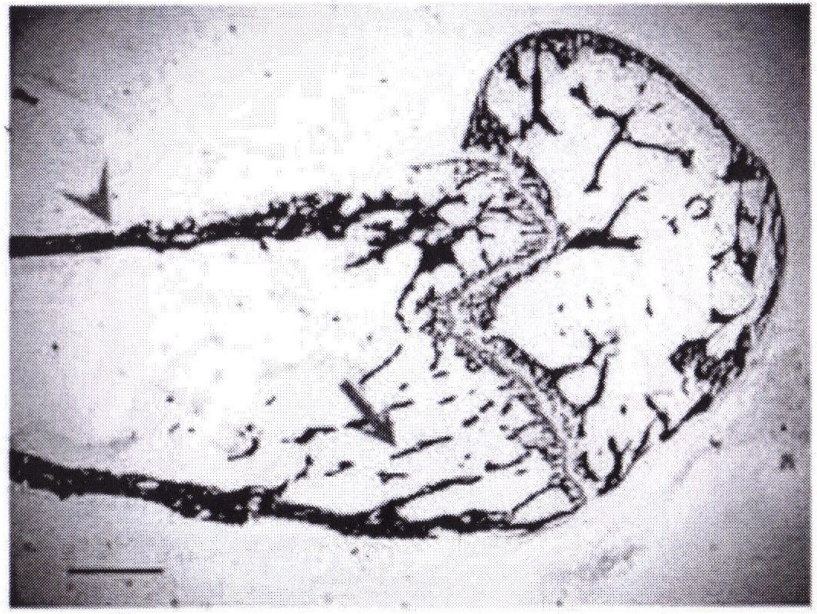
NORMONATREMIC

SOLID+DDAVP



HYPONATREMIC

LIQUID+DDAVP



Verbalis JG et al. J Bone Miner Res 25(3): 554-563, 2010

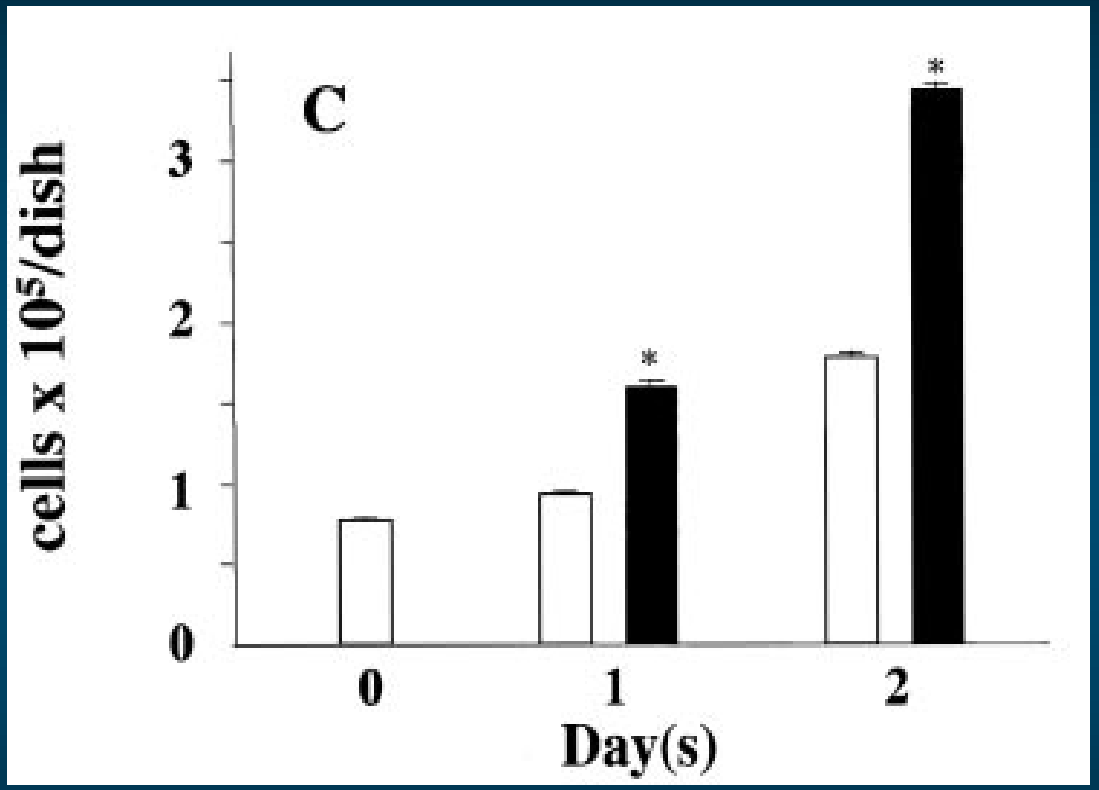
AVP AND HYPOTHALAMIC PITUITARY AXIS

- 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



Chiu T et al. Am J Physiol Cell Physiol 282: C434–C450, 2002

AVP AND INFECTION

- 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

Hepatocytes V1a-Glycolysis
Beta islet cells V1b- Insulin release
Alpha islet cells V1b- Glucagon release
CNS (Pituitary) cells V1b- ACTH release increases glucocorticoids
Adrenal Cortex V1a- increases glucocorticoids

AVP AND ACTH AND STRESS

- CRH and AVP cause ACTH to be released from pituitary

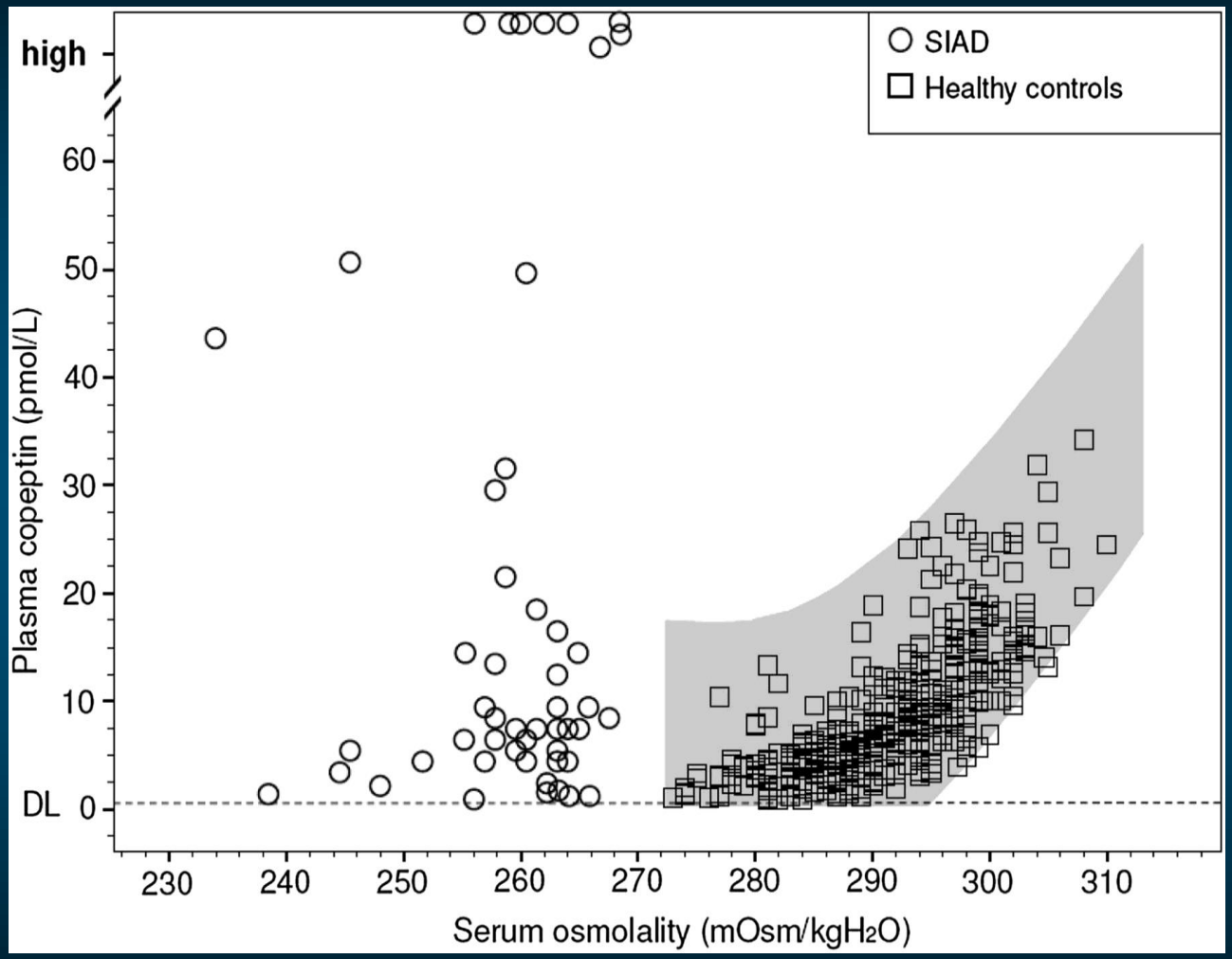
stress →V1b → releases ACTH → cortisol → glucose

- 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



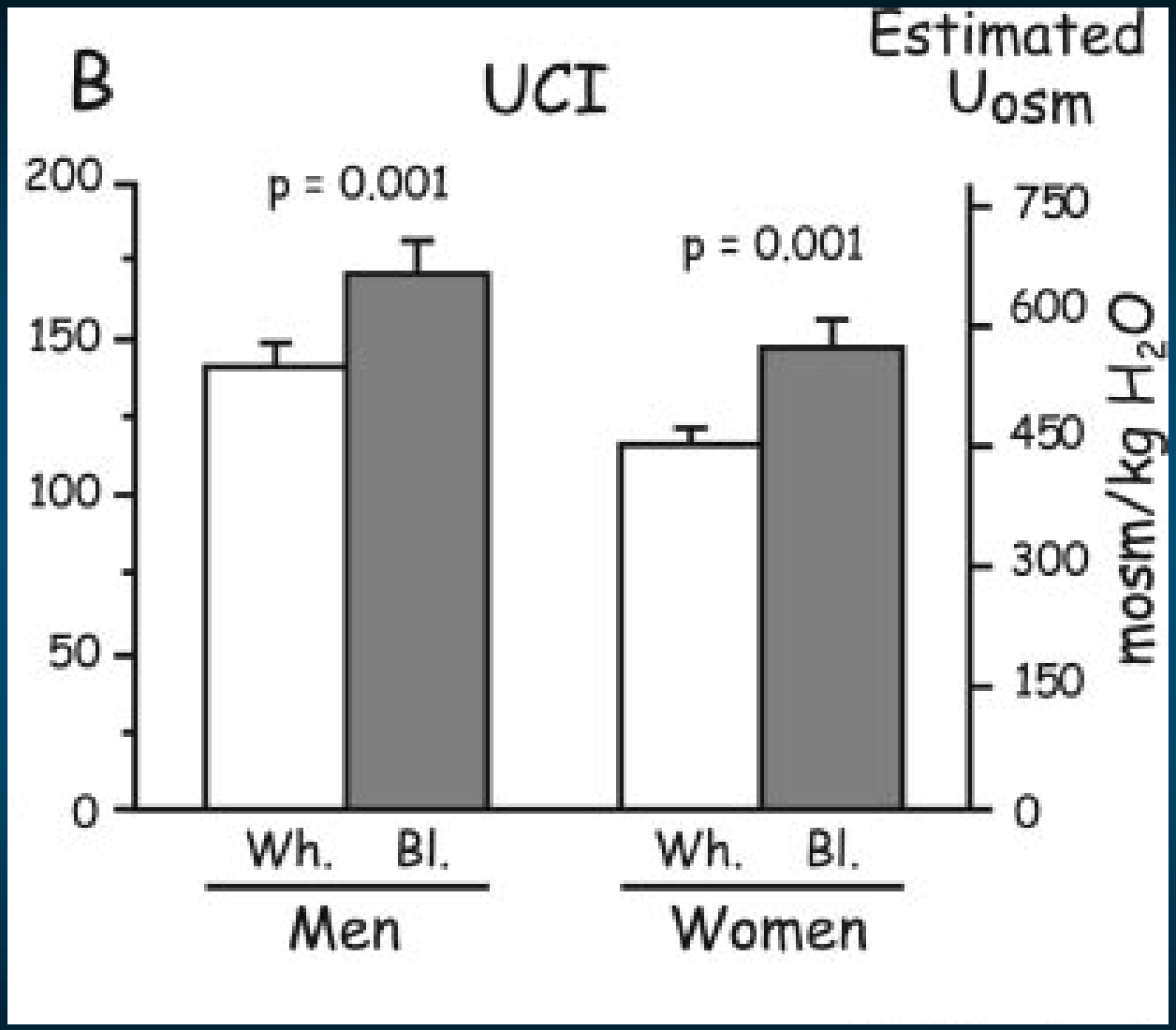
Fenske W K et al. JASN 2014;25:2376-2383

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

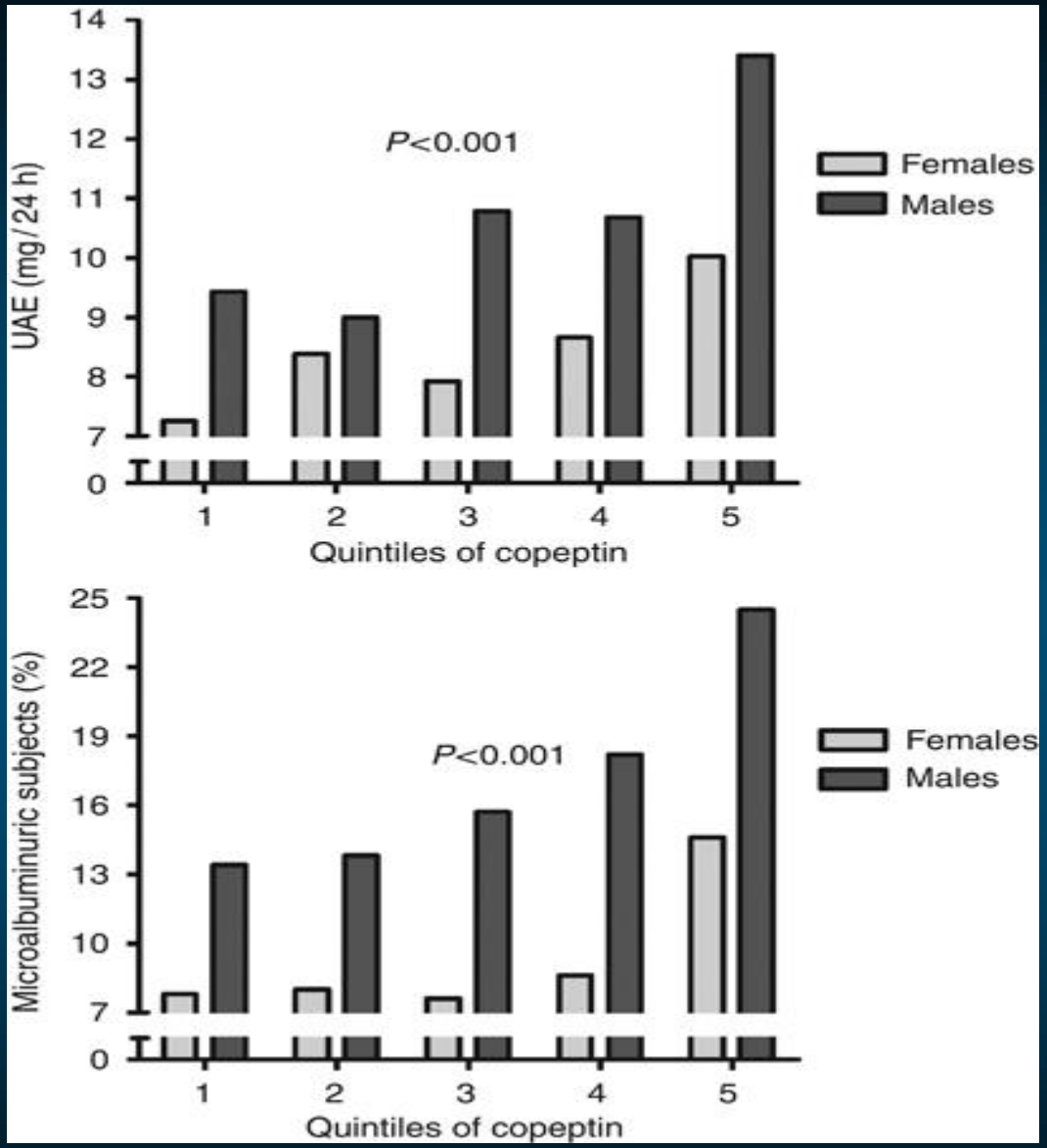
- AVP deficiency contributes to vasodilation in septic shock
- Studies over last 40 years have cited issues with sodium excretion (less efficient) in black vs white subjects
- Bankir, Parucca and MH Weinberger 2007 published a comprehensive study demonstrating more concentrated urine, higher pulse pressure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



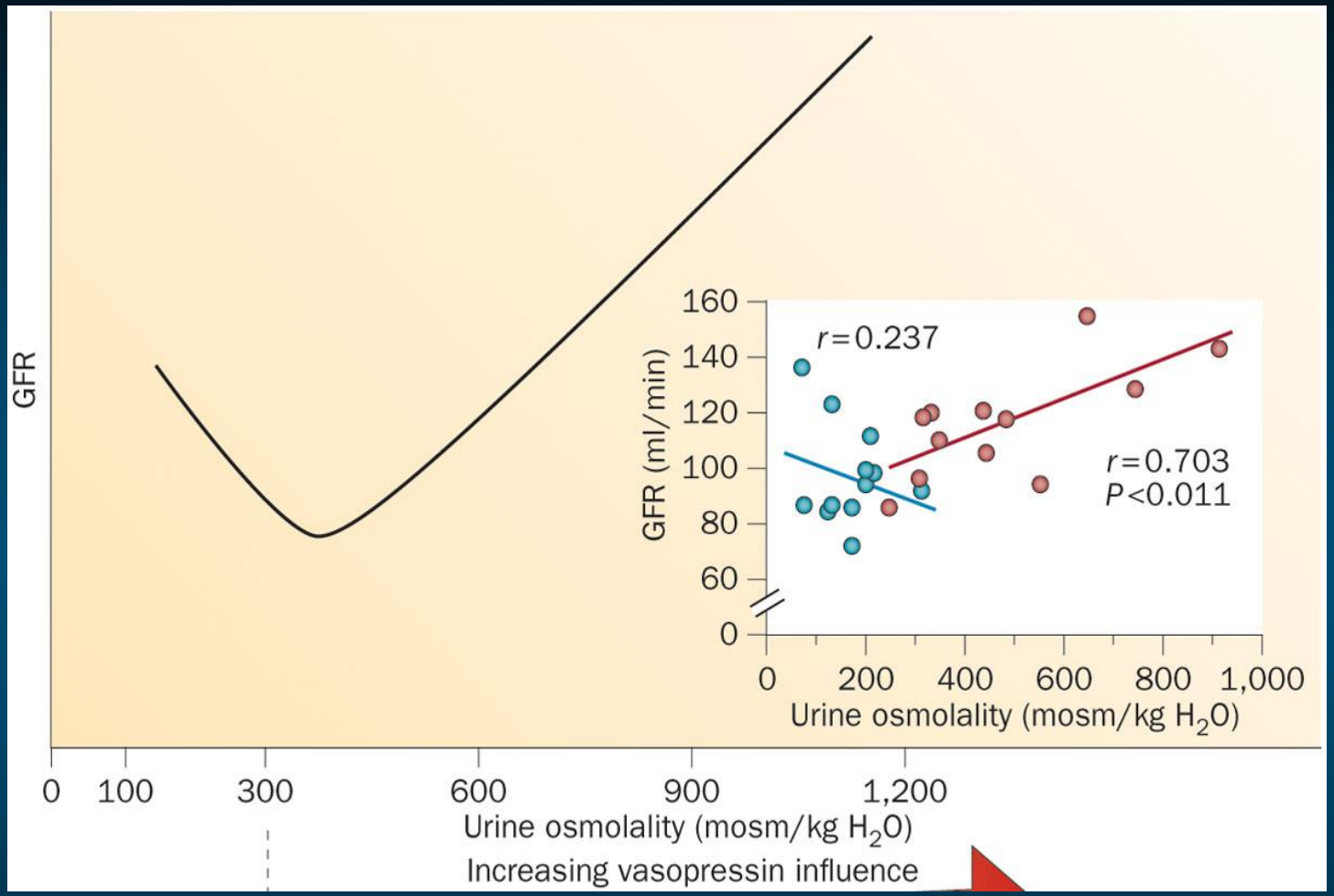
Bankir, L et al. CJASN 2: 304-312, 2007

AVP AND CKD PROGRESSION

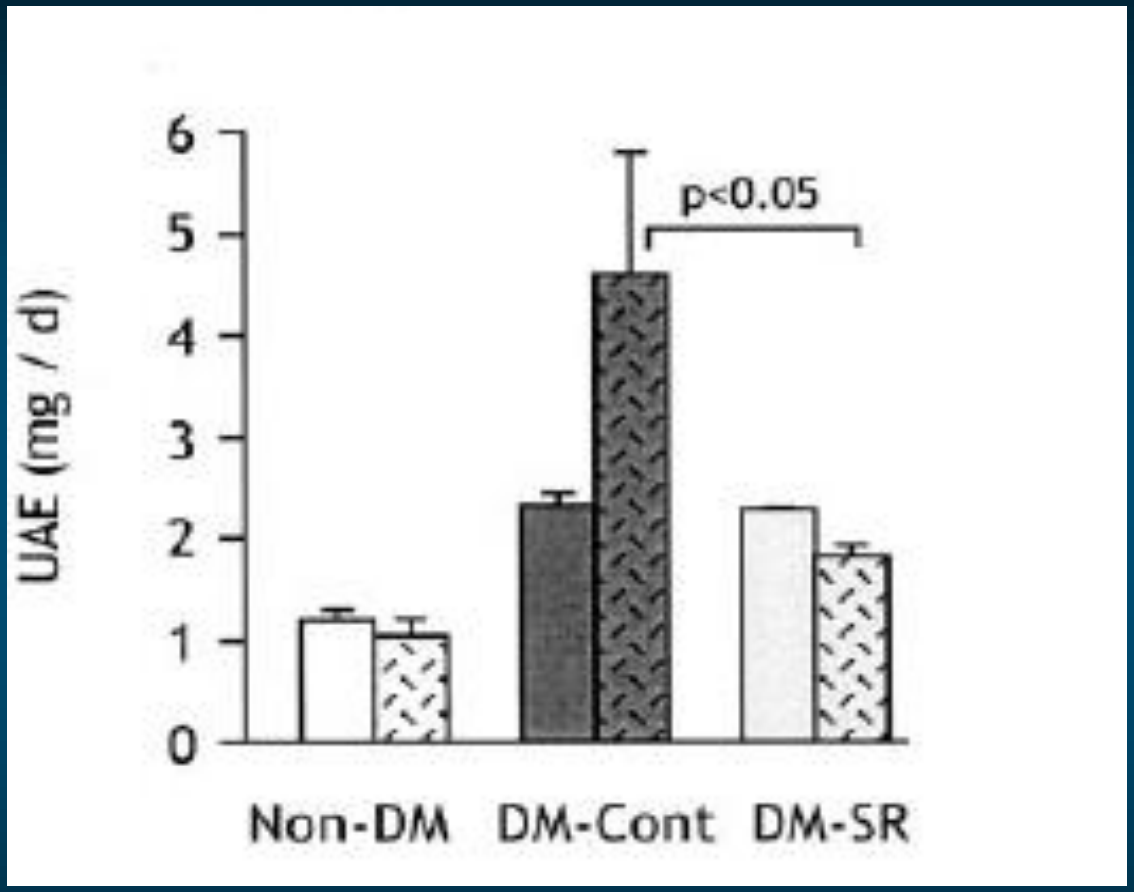
- Not only previously mentioned actions regarding diabetes mellitus and hypertension but also data relating low urine volumes and CKD progression
- AVP stimulates the renin-angiotensin system via the V2 receptor. May decrease sodium excretion and cause hyperfiltration
- DDAVP infusion increases urine osmolality and increases UAE. AVP infusion increases GFR with increased urine concentration and decreased FENA
- Efffects can be altered by ACE and V2 blockade



Meijer, E. et al. Kidney Int. 77: 29-36, 2010



Bankir, L. et al. Nat. Rev. Nephrol 9: 223-239, 2013



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