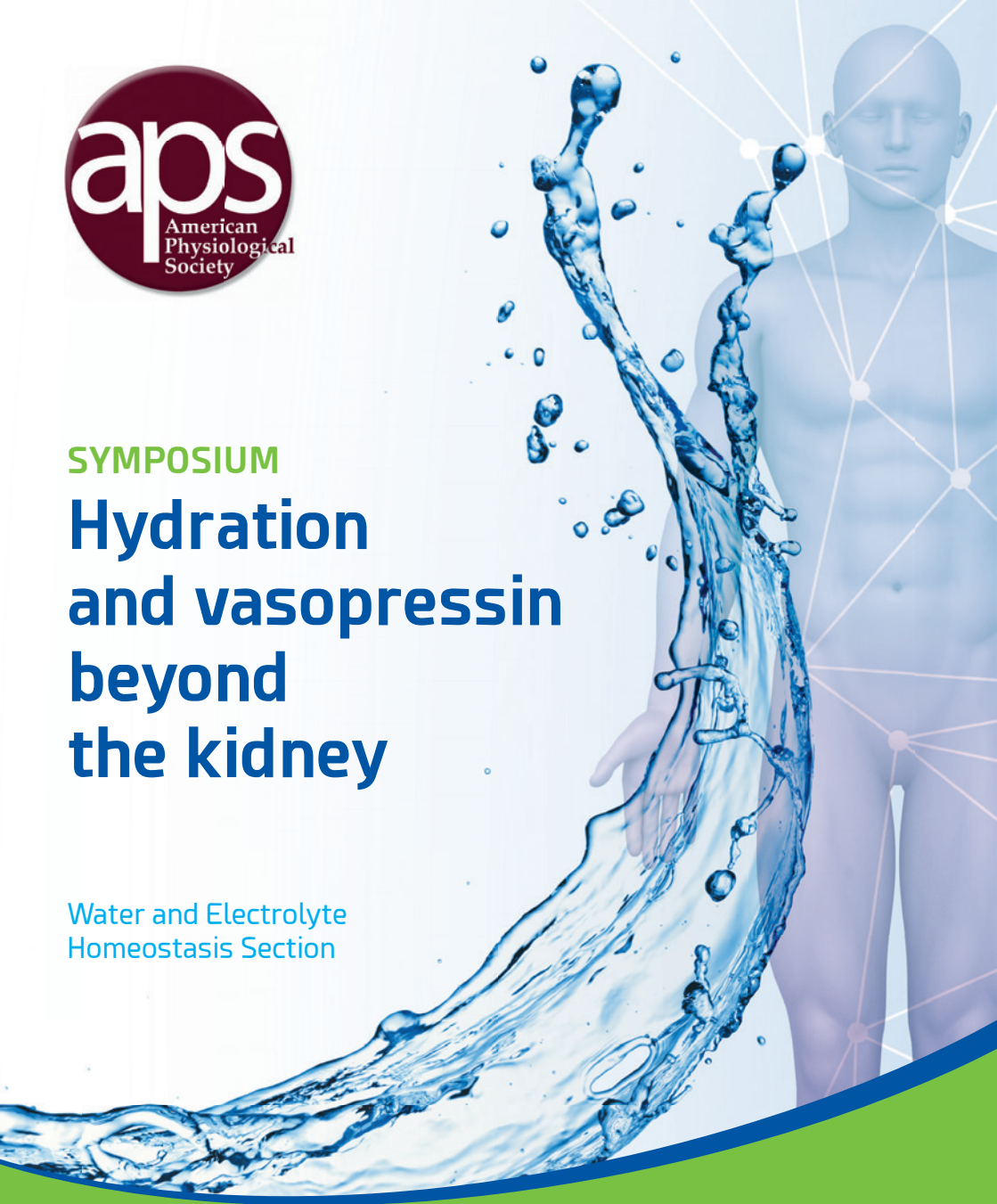

SYMPOSIUM

Hydration and vasopressin beyond the kidney

Water and Electrolyte Homeostasis Section

April 26th, 2017 • 2:30 PM - 4:30 PM
Room W190A West Building • Mc Cormick Place

DANONE NUTRICIA RESEARCH is happy to support this session

EB Experimental Biology CHICAGO 2017
TRANSFORMING THE FUTURE THROUGH SCIENCE

AGENDA

- **INTRODUCTORY TALK BY**
  Stavros A. Kavouras, Ph.D., F.A.C.S.M., F.E.C.S.S.
  University of Arkansas, USA

- **CENTRAL EFFECTS OF VASOPRESSIN IN THE BRAIN**
  Daniel G. Bichet, M.D.
  Université de Montréal, and Hôpital du Sacré-Coeur de Montréal, Montréal (Québec), Canada

- **THE VASOPRESSIN PARADOX: NOT A VASOCONSTRICTOR IN VIVO?**
  George L. Bakris, M.D., M.A., Hon. DSc., F.A.S.H., F.A.S.N., F.A.H.A.
  The University of Chicago Medicine, Chicago, IL, USA

- **VASOPRESSIN IMPACT AS A STRESS HORMONE: ANY PLACE FOR HYDRATION IMPROVEMENT?**
  Ivan Tack, M.D., Ph.D.
  Toulouse Medical School, Paul Sabatier University, France

- **FROM (DE)HYDRATION SCIENCE TOWARDS BIOMARKERS FOR HYDRATION FOR HEALTH**
  Jeanne Bottin, Ph.D.
  Danone Research, France

- **QUESTIONS & ANSWERS BY**
  Lise Bankir, Ph.D.
  The Cordeliers Research Center, University Pierre et Marie Curie, France

SESSION OVERVIEW

With the emerging evidence that high vasopressin (AVP), which is present in 25 % of the population, is an independent risk factor for diabetes and cardiometabolic disease, AVP reduction through water supplementation appears as an attractive candidate intervention to prevent diabetes and its cardiovascular complications. The hormone was identified in the fifties nevertheless only in the past decade years there is an emerging amount of evidence linking AVP-regulated water homeostasis to health outcomes. Vasopressin, first known as the antidiuretic hormone, is a key player of total water body regulation by acting on kidney to conserve water and concentrate urine in a well-described mechanism. It appears though that the effects of AVP are not limited to water balance; its actions also include inducing vasoconstriction in vascular cells, glycogenolysis in hepatocytes and ACTH release from the anterior pituitary via lower-affinity V1a and V1b receptors. From central effects to peripheral action, this session will explore the diversity of AVP's functions and multiple roles in physiology beyond the kidney. First, the session will describe the physiology and pathophysiology of central vasopressin release and perception of thirst. Second, the session will focus on key physiological functions of AVP in peripheral vascular resistance and responses to stress. Finally as plasma AVP is inversely associated with 24-hour urine volume, and associated with urine biomarkers and fluid intake, the session will give perspectives on AVP's new potential role as prognostic biomarker of renal and metabolic pathologies.

CO-CHAIRMAN

Stavros A. Kavouras, Ph.D., F.A.C.S.M., F.E.C.S.S

Department of Health, Human Performance and Recreation

University of Arkansas, USA

Dr. Stavros A. Kavouras, Ph.D., F.A.C.S.M., F.E.C.S.S. is an Associate Professor and Director of the Hydration Science Laboratory at the University of Arkansas & Adjunct Professor in Medicine at the University of Arkansas Medical Sciences, Division of Endocrinology. His laboratory is studying the mechanisms by which water intake affects health and performance. Dr. Kavouras is the author of more than 100 peer review articles and he has given lectures in 28 countries. He is a section Editor of the European Journal of Nutrition and program coordinator for the Exercise Science program. Dr. Kavouras is a Fellow of the American College of Sports Medicine & the European College of Sports Science as well as elected member of the American Physiological Society, the American Society of Nutrition, and the Obesity Society.

CO-CHAIRMAN

Lise Bankir, Ph.D.

Inserm U1138, The Cordeliers Research Center

University Pierre et Marie Curie, France

Dr. Lise Bankir, Ph.D. is Directeur de Recherche Emeritus at INSERM, Centre de Recherche des Cordeliers, Paris, France. She graduated in Paris and got her Master and Ph.D. in the University of Paris-Sorbonne.
Most of her career has been devoted to experimental and applied research in renal physiology and pathophysiology. She initially got interested in the anatomical and functional adaptations of the kidney that allow mammals to excrete electrolytes and soluble metabolic endproducts in concentrated urine. She and her group studied the consequences on the kidney of the sustained action of the antidiuretic hormone vasopressin or of a protein-rich diet that imposes on the kidney a more intense concentrating activity. These experimental studies revealed that the long term action of vasopressin on the kidney, besides its advantageous effects on water economy, has adverse consequences on the incidence and/or progression of chronic kidney disease, diabetic nephropathy and hypertension. Several studies are now confirming this pathophysiologic link in humans. Dr. Lise Bankir has published over 150 original papers and invited reviews in peer-reviewed journals, and written several book chapters. She is a member of several national and international Societies of Nephrology and Biology. In 2011, she received the Berliner Award from the American Physiological Society and the Collery Award from the French National Academy of Medecine.

Daniel Bichet, M.D.

Professor of Medicine, Pharmacology and Physiology,
Université de Montréal, and Hôpital du Sacré-Coeur de Montréal,
Montréal (Québec), Canada

Dr. Daniel G. Bichet, M.D. is Professor de Medicine Pharmacology and Physiology at University of Montreal and a nephrologist à l'Hôpital du Sacré-Coeur de Montréal. He obtained his medical degree at the Université de Besançon (France) and completed additional clinical training at University of Montreal and McGill University affiliated hospitals. He did a research fellowship at the University of Colorado Health Sciences Center under the mentorship of Dr. Robert W. Schrier. He received the Jonathan Ballon Award of the Quebec Heart and Stroke Foundation and obtained a Canadian Institutes of Health Research Chair in Genetics of Renal Diseases from 2003 to 2010. Dr. Bichet's research includes fundamental life-sustaining homeostatic networks for water and osmotic pressure balance in human physiology. His laboratory is contributing to the prevention of extreme dehydration states in children with polyuric disorders (Central and Nephrogenic Diabetes Insipidus). Dr. Bichet received the Medal of the Kidney Foundation of Canada in 1998, a Doctorat Honoris Causa from the University of Nancy (France) in 1999, and the Jean Hamburger Medal (the highest distinction of the European Society of Nephrology) in 2010.

• CENTRAL EFFECTS OF VASOPRESSIN IN THE BRAIN

Recent experiments using optogenetic tools in awake animals demonstrate that a substantial fraction of normal drinking behavior and vasopressin release is not regulated by changes in the blood directly, and instead appears to anticipate homeostatic changes before they occur. Anticipatory signals for thirst and vasopressin release converge on the same homeostatic neurons, subfornical (SFO) neurons, specifically, that monitor the tonicity of blood . Subfornical organ excitatory neurons (SFONos1) activated by water restriction, had their activity rapidly returning to baseline after water access well before any measurable change in plasma osmolality. This rapid anticipatory response to drinking has been suggested by blood-oxygen-level-dependent (BOLD signal) measurements during thirst stimulation in humans where the BOLD signal from the anterior cingulate cortex area, known to be responsible for the conscious perception of thirst, decreased rapidly after water consumption well before any systemic absorption of water. There is a delay of around ten minutes between the ingestion of water and its full absorption into the bloodstream and these new data are explaining how drinking can quench thirst within seconds, long before the ingested water has had time to alter the blood volume or osmolality. New data also demonstrate that dendritic release of vasopressin in the paraventricular nucleus (PVN) is perceived by vasopressin V1a receptors on pre-autonomic neurons with consequent stimulation of renal afferents, a central control of volemia: the lamina terminalis and autonomic nervous system are separated by just two synapses: excitatory neurons in the lamina terminalis project to neurons in the PVN which, in turn, sends descending projections to autonomic regions of the hindbrain and spinal cord.

REFERENCES: Zimmerman CA, Lin YC, Leib DE, et al. Thirst neurons anticipate the homeostatic consequences of eating and drinking. Nature. 2016;537(7622):680-684. Mandelblat-Cerf Y, Kim A, Burgess CR, et al. Bidirectional Anticipation of Future Osmotic Challenges by Vasopressin Neurons. Neuron. 2017;93(1):57-65. Son SJ, Filosa JA, Potapenko ES, et al. Dendritic peptide release mediates interpopulation crosstalk between neurosecretory and preautonomic networks. Neuron. 2013;78(6):1036-1049.

George L. Bakris,
M.D., M.A., Hon. DSc., F.A.S.H., F.A.S.N., F.A.H.A. ,

Professor of Medicine (tenured),
Director of the ASH Comprehensive Hypertension Center,

The University of Chicago Medicine, Chicago, IL, USA

Dr. George L. Bakris M.D., M.A., Hon. DSc., F.A.S.H., F.A.S.N., F.A.H.A. received his medical degree from the Rosalind Franklin School of Medicine and completed residency in Internal Medicine at the Mayo Graduate School of Medicine where he also completed a research fellowship in Physiology and Biophysics. He then completed fellowships in Nephrology and Clinical Pharmacology at the University of Chicago. From 1988 to 1991, he served as Director of Renal Research at the Ochsner Clinic and had faculty appointments in the Departments of Medicine and Physiology at Tulane University School of Medicine. He later was Professor and Vice Chairman of Preventive Medicine and Director of the Rush University Hypertension Center in Chicago from 1993 until 2006. Currently, he is a Professor of Medicine and Director of the ASH Comprehensive Hypertension Center in the Department of Medicine at the University of Chicago Medicine. Dr. Bakris has published over 800 peer-reviewed articles and book chapters in the areas of diabetic kidney disease, hypertension and progression of nephropathy. He is the Editor or Co-Editor of 20 books, in the areas of Kidney Disease Progression and Diabetes as well as the new 3rd edition of Hypertension: A Companion to Braunwald's The Heart. Additionally, he is an Associate Editor of the International Textbook of Cardiology. He was a member of the NIH National High Blood Pressure Education Program Working Group on Hypertension and Renal Disease (1994). He also serves as a special government expert to the Cardio-renal Advisory Board of the FDA and to CMS. He was a co-principal investigator on the NIH Clinical Research training grant for clinical research (K30) (1999-2004). He chaired the first National Kidney Foundation Consensus report on blood pressure and impact on renal disease progression (2000). He has also served on many national guideline committees including: The Joint National Committee Writing Groups VI & 7 (1997, 2003), the JNC 7 executive committee (2003), the American Diabetes Association Clinical Practice Guideline Committee (2002-2004), the National Kidney Foundation (K-DOQI) Blood Pressure Guideline committee (2002-2004 & 2013), (K-DOQI) Diabetes Guideline committee (2003-2005 & 2014), Chair, ADA BP Consensus Report (2016) and writing committee ACC/AHA Resistant Hypertension Guidelines (2016-2017). Dr. Bakris is the past-president of the American College of Clinical Pharmacology (2000-2002) and the American Society of Hypertension (ASH). He is the current Editor-in-Chief, Am J Nephrology, Editor-in-Chief- Up-to-Date, Nephrology section, Hypertension Section Editor Up-to-Date and Assoc. Ed of Diabetes Care. He serves on more than 18 editorial boards including Nephrology, Dialysis & Transplant, Hypertension, J Hypertension and J American Soc. Hypertension.

• THE VASOPRESSIN PARADOX: NOT A VASOCONSTRICTOR IN VIVO?

The hemodynamic effects of vasopressin are complex and modulated not only by serum osmolality but also the vascular homeostasis of the person. Vasopressin works through stimulation of V1 and V2 (aquaporin)receptors. Stimulation of V1 receptors traditionally yield vasoconstriction and stimulation of V2 receptor yield an antidiuretic effect. The vasoconstricting effect of vasopressin on the V1 receptor can be blocked with a calcium channel blocker since it is a calcium mediated response of vasopressin responsible for vasoconstriction. Persons who are well or overhydrated tend to have low levels of vasopressin and the converse is also true.

There are two circulatory beds that are of note where V2 receptors also yield a vasodilator response. One is the afferent arteriole of the kidney and the other is the cerebral circulation. Injection of vasopressin into the cerebral vessels of dogs showed a 30-50 % vasodilatory response, a response modulated by nitric oxide. Rats infused with sequential doses of AVP in 30-min increments showed that sub pressor infusion resulted in progressive renal vasodilation. However, at high doses, BP increased 29 + 6 mm Hg and RVR increased. This vasodilatory response is modulated by nitric oxide (NO). Infusion of AVP doubled urinary cyclic GMP excretion, a marker for renal NO synthesis. This relationship between AVP and NO is further evidenced by studies in rats given L-NAME before infusion of AVP. L-NAME increased BP 22+3 mm Hg, after L-NAME, no dose of AVP had any further effect on either BP, RBF, or RVR. In separate studies in the dog kidney, the V2 stimulated vasodilator response was blocked by a V2 receptor antagonist. Moreover, in a norepinephrine constriction canine model, use of desmopressin resulted in a vasodilation. Lastly, in a salt sensitive rat use of V2 receptor blockade resulted in increasing BP in a dose response manner. Thus, V2 receptor stimulation can result in vasodilation in a dose dependent manner in certain arterial beds.

Ivan Tack, M.D., Ph.D.

Professor of Physiology, Head of the Clinical Physiology Department,

Toulouse Medical School, Paul Sabatier University, France

Professor Ivan Tack, M.D., Ph.D. is a nephrologist, Head of the Dpt of Clinical Physiology in Rangueil hospital since 2006 and Chairman of the Dpt of Physiology at Paul Sabatier University – Toulouse School of Medicine, France. He experienced a post-doctoral fellowship at University of Miami School of Medicine, Dpt of Nephrology (USA) working on pathophysiology of diabetic nephropathy. His clinical activity mostly focuses on water and electrolytes disorders, inherited tubular diseases and metabolic impact of nutritional disorders, including renal stone diseases and osteoporosis. Concomitantly he is involved in experimental research (INSERM Unity 1048, Toulouse) with a focus on early protection from renal diseases based on in vivo experimental modelling (main models: diabetic nephropathy, post-hemorrhagic acute kidney injury, renal stone disease in murine). He has authored/co-authored over 80 peer-reviewed scientific articles and regularly contributes to the development of French Health High Authority program. Professor Tack is a member of the American Society of Nephrology, American Physiological Society and also collaborates with Danone Nutritia Research since 2007 as a member of the Scientific Advisory Board (Water Division).

• VASOPRESSIN IMPACT AS A STRESS HORMONE: ANY PLACE FOR HYDRATION IMPROVEMENT?

• THE MULTIPLE FACES OF VASOPRESSIN...

Since the discovery of endocrine roles of pituitary gland, at the turn of the 20th century, it took one century and two Nobel prizes to identify the small peptide arginine vasopressin (AVP) and to describe its main functions and regulatory pathways. Since the beginning, AVP has confused researchers by the duality of its actions. This hormone is "classically" responsible for renal water saving at low concentration and for blood maintenance of pressure during hypovolemia at higher concentration. Indeed, AVP is involved in wide range of physiological or clinical situations at the frontier of "stress". Whereas beneficial at short term, the impact of its prolonged and/or intense AVP secretion becomes questioned.

• VASOPRESSIN IN EVERYDAY LIFE: THE HORMONE OF RENAL WATER ECONOMY

Water turn-over is variable, as both fluid intake and output may vary up to tenfold. Osmotic stimulation of AVP activates renal vasopressin V2 receptors expressed in the distal part of nephron, inducing apical membrane expression of Aquaporine-2 water channel and concomitant water reabsorption. Thus, AVP modulates urine volume from 0.5 to up to 12 – 15 liters/day. When renal water saving is insufficient to limit the raise of plasma osmolality, thirst provides a complementary pathway to restore water balance by adjusting drinking behavior. If oral hydration is delayed or insufficient, AVP will continue to increase largely above level that elicits maximum urine concentration, resulting in potential hem odynamic and metabolic effects.

• VASOPRESSIN IS ALSO A STRESS HORMONE

Beside the role of V2 receptor on renal water economy, vasopressin pathway involves two other receptors: 1) V1a that is expressed in vascular smooth muscle cells, hepatocytes and adrenal cortex where its activation respectively produces powerful vasoconstriction, glycolysis and stimulates both aldosterone and glucocorticoid secretion; 2) V1b receptor that is mostly expressed in anterior pituitary and islet cells of Langerhans where its activation respectively stimulates adrenocorticotropin (ACTH) secretion and modulates both insulin and glucagon secretions. Practically, vasopressin receptor stimulation, especially at high AVP concentration, not only ensures plasma volume and blood pressure, protecting tissue perfusion, but it also raises glycaemia and recruits the glucocorticoid axis. Taken together, these effects confer stress hormone status to vasopressin, along with catecholamine and glucocorticoids. Beyond the miraculous potency of their acute recruitment during fight and flight response, stress hormones have also proven to be detrimental when chronically recruited. Improvement of the biological approach of Vasopressin pathway these past years has provided evidence for increased AVP secretion in multiple physiological (pain, fair, exercise, labor and delivery…) and clinical (fever, nausea, vomiting, diabetes, uncontrolled hypertension, heart ischemia…) situations. In these cases, AVP concentrations are often above that of renal water saving without clear evidence of hypovolemia. This raise the question of its long term impact.

• THE DARK SIDE OF VASOPRESSIN: COULD ITS LONG TERM RECRUITMENT BE DETRIMENTAL?

Water homeostasis has been considered as almost perfect for decades, thus poor attention has been paid to the significance of physiological but chronically elevated plasma AVP concentrations in humans. However, there is a now evidence for relationships between: 1) urine volume or fluid intake and the risk of chronic kidney disease progression; 2) antidiuresis, AVP (or its surrogate marker Copeptin) and the risk to develop type 2 diabetes or components of the metabolic syndrome. Because of their high prevalence, such potential impacts require additional attention, claiming for mechanistic but also interventional studies.

• CAN IMPROVEMENT OF HYDRATION COUNTERACT CHRONIC IMPACT OF VASOPRESSIN?

Due to the duality of vasopressin that becomes a stress hormone when increased, its marked and/or prolonged recruitment has a potential cost for the kidney, and likely for metabolic and cardiovascular health. This could be the case during various physiological and clinical circumstances such as prolonged renal water economy, especially in case of prior CKD, but also during poorly controlled diabetes or hypertension. Medical knowledge in this field is only emerging and a relationship is far from proving causality. However, proofs of concept are already sufficient to encourage people to drink at least enough water to meet published dietary reference values, and to propose interventional randomized controlled hydration study in the most exposed situations. Two main questions remained to be answered: 1) Can improvement of hydration prevent health impact of AVP even in circumstances where its stimulation is independent of osmotic regulation? 2) What does drinking "enough" practically mean regarding potential health benefits?

Jeanne Bottin, Ph.D.

Hydration Physiology Scientist,

Danone Research, France

Dr. Jeanne Bottin earned her MS in food science with a specialization in human nutrition and biology from AgroParisTech, France and her PhD in Nutrition and Endocrinology from Imperial College London, UK. Currently at Danone Research, one of Jeanne's roles is to study the relationships between water intake, hydration physiology, and cognitive function in children. Prior to joining Danone Research, Jeanne studied appetite regulation in overweight, obese and bariatric patients. She has conducted several clinical trials in the fields of nutrition, bariatric surgery, body composition, nutrient intake, and metabolism. She has an interest in public health and has worked in Nigeria on nutritional supplementation, growth, and cognition in children.

• FROM (DE)HYDRATION SCIENCE TOWARDS BIOMARKERS FOR HYDRATION FOR HEALTH

Over the past 10 years, the literature on hydration biomarkers has evolved considerably – from (de)hydration assessment towards are more global definition of biomarkers of hydration in daily life. This shift in thinking about hydration markers was largely driven by examining differences between otherwise healthy individuals whose habitual, ad libitum drinking habits differ, and by identifying physiological changes in low-volume drinkers who increase their water intake. Aside from obvious differences in urinary volume and concentration, a growing body of evidence is emerging that links differences in fluid intake with small, but biologically significant, differences in vasopressin (copeptin), glomerular filtration rate, and metabolic markers. Combined, these pieces of the puzzle begin to form a picture of how much water intake should be considered adequate for health. Finally, if adequate water intake can play a role in maintaining health, how can we tell if we are drinking enough? Urine output is easily-measured, and can take into account differences in daily physical activity, climate, dietary solute load, and other factors that influence daily water needs. Reasonable targets will be proposed for urine osmolality (500 mOsm/kg), specific gravity, and color that may be used by researchers, clinicians, and even individuals as simple indicators of optimal hydration.

DANONE NUTRICIA RESEARCH
is happy to support this session

aps American Physiological Society

DANONE NUTRICIA RESEARCH