suggest a class of glucose lowering drugs that can reduce cardiovascular morbidity and mortality in high-risk type 2 diabetic patients. However, the reductions in haemoglobin A1c were modest and it is unlikely that this change in glycaemic control could affect cardiovascular events within such a short period of time. The rapid effects of SGLT2 inhibitors on blood pressure, body weight (likely to reflect fluid loss and reduced tissue mass), and cardiovascular events suggest that hemodynamic effect contributes to the benefit observed with SGLT2 inhibitors. However, several mechanisms may be important for the beneficial effects on cardiovascular outcome [5-7]. SGLT2 inhibitors were developed to improve glucose control in diabetic patients. It will be interesting to see the results of ongoing studies, examining the effects of SGLT2 inhibitors on cardiovascular events in patients with cardiovascular disease but with no diabetes. These and other studies will eventually clarify if SGLT2 inhibitors should be considered glucose lowering drugs for diabetic patients with additional cardiovascular protective effects, cardiovascular (antihypertensive and/or diuretic) drugs with additional glucose lowering properties, or renal protective drugs with additional cardiovascular and glucose lowering effects. The issue is not trivial, for patients, care providers, regulatory authorities, and for the pharmaceutical industry.

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- Thomas Kahan

Hot Off the Press

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Increased salt consumption induces body water conservation and decreases fluid intake

Rakova et al. (2017) *J Clin Invest* 127(5) 1932-1943 DOI: 10.1172/JCI88530

This particular article made international headlines in May when the New York Times and other media outlets highlighted how the results could change our understanding of the body's handling of sodium [1]. Current dogma is that increased salt intake leads to increased thirst which stimulates fluid intake. However there had been prior studies which have questioned this relationship [2]. This study, and other related ones from the same study cohort, are quite comprehensive and could be the subject of much larger and more comprehensive summaries. I will restrict my summary to the major highlights of the study.

The primary goal of this study was to examine the relationship between salt intake and urine volume and the authors took a very innovative approach.

The authors took advantage of two simulated Mars missions being conducted by the European Space Agency and the

Russian Institute for Biomedical Problems (IBMP) [3]. The interest in sodium/water balance for such a mission likely stems from the potential need for extreme water conservation during a prospective mission to Mars.

Mars 105 consisted of 12 men in simulated space flight for 105 days while Mars 520 had men in flight for 520 days.

For the Mars 105 study salt intake was followed over 105 days with sodium successively adjusted from 12 g/day to 9 g/day and then 6 g/day after intervals of at least 29 days. On the Mars 520 study (conducted over 205 days) the intake was adjusted from 12 g/day to 9 g/day and 6 g/day and then back to 12 g/day, again with the interval between changes being at least 29 days. Subjects had access to fluids (tap water, tea, coffee, juice and milk) in an unrestricted fashion but calories were controlled and nutrients were described as being "maintained constant throughout the study". Urine was collected over 24 hours. The authors excluded subjects from analysis when their weekly urinary sodium recovery was repeatedly less than 80% of sodium intake or when the subjects did not adhere to the daily menu plans. The strict criteria for inclusion resulted in the exclusion of 2/14 subjects from the study.

Consistent with what would be expected, the authors observed that higher intake of salt led to more salt in the urine. By contrast, with respect to water intake what was observed was a decrease as dietary salt increased which is counterintuitive based on existing paradigms. As an explanation, the authors looked at free water generation and showed that at higher salt concentrations free water generation also increased. Furthermore, increased cortisol levels were associated with greater urine volume without increased water intake which suggests that the increased urine volume was due to endogenously created water.

The authors proposed three hypothesis to explain their results.

Hypothesis 1: Increasing salt intake promotes accrual of endogenous water.

Hypothesis 2: Dietary salt modulates endogenous infradian-rhythmical control of osmolyte and water accrual and release.

Hypothesis 3: High salt intake induces glucocorticoid-driven metabolic water production.

Like all studies, the data shown here need to be replicated in larger populations (if such a study is even possible), however the methodology appears to be rigorous and, as such, the results do call into question current views on sodium and water balance.

Finally, a provocative aspect of this manuscript was the fact that the authors called into question the validity of sodium/salt excretion as a surrogate for intake. In referencing prior work from the same study population [4] the authors quite provocatively stated that "We are not convinced that epidemiological studies and information policy, which rely on associations among food intake, beverage consumption, and salt content in the urine to study a functional relationship among salt intake, soft drink consumption, and obesity in populations, rest on valid physiological and methodological assumptions". These are strong words coming from a study of 12 individuals, but perhaps do need to be given some consideration.

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1 https://www.nytimes.com/2017/05/08/health/salt-health-effects.html?_r=0

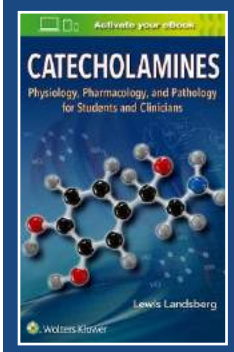
2 Luft FC *et al.* (1983). The effect of dietary sodium and protein on urine volume and water intake. *J Lab Clin Med* 101(4) 605-610.

3 http://www.esa.int/Our_Activities/Human_Spaceflight/Mars500/Mars500_study_overview

4 Lerchl K *et al.* (2015) Agreement between twenty-four hour salt ingestion and sodium excretion in a controlled environment. *Hypertension* 66(4) 850-857.

- Dylan Burger

Catecholamines – Physiology, Pharmacology, and Pathology for Students and Clinicians



Dr. Lewis Landsberg (Chicago) has written a new booklet on catecholamines (Wolters Kluwer, 2017 pp 1-147), which kept me company on a recent long flight. It is a comprehensive and clinically relevant monograph, which provides an authoritative summary of how catecholamines regulate bodily functions in health and disease, as well as how this knowledge has generated an extensive pharmacopeia of widely-used drugs. It gave me solid information and guidance on these complex hormones and helped me understand the sympathoadrenal system better than before. The booklet is indeed worth reading and I recommend you do so! Dr. Landsberg (former Professor at Harvard Medical School and former Dean of North Western Medical School in Chicago) is the chairman of the Board of Management of the Journal of Hypertension.

Lars H Lindholm, Editor