Special Issue
Selected Abstracts of the III International Caparica Conference on Urine OMICS and Nephromics (URINOMICS 2017)

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III International Caparica Conference on Urine OMICS and Nephromics
(URINOMICS 2017)

Caparica – Lisbon, Portugal – 18th-21st September 2017

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A methodological Journal

SELECTED ABSTRACTS OF THE III INTERNATIONAL CAPARICA CONFERENCE ON URINE OMICS AND NEPHROMICS (URINOMICS 2017)

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SPECIAL ISSUE: SELECTED ABSTRACTS OF THE III INTERNATIONAL CAPARICA CONFERENCE ON URINE OMICS AND NEPHROMICS (URINOMICS 2017)

Targets in urinalysis for Wilson's disease

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ABSTRACT

Urine is a commonly used specimen for analysis with clinical importance to detect and manage a wide range of disorders, prevalent and rare. Laboratory urine samples are classified by the type of collection or by the collection procedure – first and second morning urine, a random urine portion, 24-hour urine sample and etc. Results interpretations are useful clinical tools.

Harmonization in laboratory medicine requires deep knowledge of all steps in total testing process - from pre pre-analytical to post – examination. Some critical factors (proper time for sampling; sample type; sample container and volume; transport and storage with appropriate time and temperature) may serve as quality indicators. An effective urine diagnosing strategy should be based on standard procedures for collection, transport and analysis.

Underlined impact of urine analysis in Wilson's disease (WD) management is the reason for our special interest in this biological specimen – sample preparation before analysis, analytical determination of copper in urine, frequency of urine examinations to monitor the adequacy of chelating therapy, prevention of probable adverse effects as nephrotic syndrome, effective clinical laboratory approach as whole in this very complicated clinical situation.

Our experience defines urine as a delicate but stabile biological matrix for copper analysis. The stability is rather higher in the case of D-penicillamine administration (1000 mg/day) in comparison to urine control group for both studied temperature regimens (ambient 15-25°C and refrigeration 2-8°C). Plastic containers and tubes are pointedly suitable for sample collection and pre-analytical preparation with guarantee the lack of contamination. Flame atomic absorption is acceptable analytical method for copper urine analysis in concentration range Cu ≥ 0.23 μmol/L (Limit of detection). Monitoring of urine protein concentration in 24-hour sample is recommended at least every 6 months in WD patients on D-penicillamine to prevent eventual development of nephrotic syndrome - rare but severe adverse effect.

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Increased Phosphate excretion in critically ill children

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ABSTRACT

Objective: To determine the prevalence of hypophosphatemia in critically ill children; to determine the mechanism of hypophosphatemia in critically ill children.

Methods: Levels of Serum phosphate, phosphate intake, renal phosphate handling indices and blood gases were measured on days 1, 3, 7 and 10 of PICU stay. Hypophosphatemia was defined as any serum phosphorus <3.8 mg/dL for children younger than 2 years and <3.5 mg/dL for children 2 years or older. Renal phosphate loss was assessed using TmP/GFR.

Results: Prevalence of hypophosphatemia was 71.6% (95% CI: 64.6-78.6). Renal phosphate threshold was significantly lower on all the days in hypophosphatemic group compared to that of non-hypophosphatemic. No statistically significant difference in the amount of phosphate intake was seen in both the groups. (Table 1)

Conclusion: Hypophosphatemia is highly prevalent in critically ill children. Increased phosphate loss in urine is one of the mechanism responsible for hypophosphatemia in critically ill children.

Acknowledgments:

The authors are thankful to enrolled children and their parents, lab clinicians and on duty resident doctors.

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Table 1

Variables	Hypophosphatemia	No hypophosphatemia	P value
D1 Phosphate intake (mg/kg)	0.8 ± 6.1	0.5 ± 2.9	0.86
D1 Calorie intake (Cal/kg)	3.1 ± 2.1	3.2 ± 2.4	0.50
D3 Phosphate intake (mg/kg)	14.4 ± 12.4	24.4 ± 16.8	**0.04**
D3 Calorie intake (Cal/kg)	8.1 ± 6.9	9.1 ± 8.5	0.6
D7 Phosphate intake (mg/kg)	25.9 ± 21.1	33.7 ± 22.5	0.26
D7 Calorie intake (Cal/kg)	18.4 ± 12.7	24.3 ± 16.5	0.14
D10 Phosphate intake (mg/kg)	31.2 ± 22.1	48.1 ± 28.5	0.39
D10 Calorie intake (Cal/kg)	29.4 ± 16.5	35.3 ± 21.0	0.50
Serum pH, mean ± SD			
D1	7.33 ± 0.01	7.31 ± 0.01	0.16
D3	7.37 ± 0.01	7.35 ± 0.01	0.28
D7	7.38 ± 0.01	7.36 ± 0.01	0.32
D10	7.38 ± 0.01	7.37 ± 0.01	0.45
$TmPO_4$/GFR(mg/dL),median(IQR)			
D1	2.3 (1.8, 3.4) (n=89)	4.3 (3.4, 5.5) (n=30)	**<0.001**
D3	2.2 (1.5, 2.8) (n=78)	4.1 (3.2, 4.9) (n=20)	**<0.001**
D7	2.0 (1.2, 2.9) (n=49)	4.2 (2.8, 5.5) (n=11)	**<0.001**
D10	1.7 (1.2, 3.2) (n=35)	4.4 (3.4, 5.2) (n=9)	**<0.001**
PTH,pg/mL,median(IQR)			
D1 Serum PTH	31.4 (17.8, 54.9)	43.5 (18.2, 60.6)	0.20

IQR: Interquartile range SD: Standard deviation

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Towards early detection of pancreatic cancer in urine

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ABSTRACT

With >8,500 deaths in the UK, Pancreatic Ductal AdenoCarcinoma (PDAC) is currently the 5th leading cause of cancer-related death, but predicted to become the second by 2030 [1]. PDAC is almost always diagnosed at an advanced stage when curative surgery is no longer possible and patients die within 6-8 months. Development of a test for early detection of this malignancy would therefore highly likely have a huge impact on survival of PDAC patients. For the last several years we have been interrogating urine samples for proteins, miRNAs and recently volatile organic compounds in order to find the biomarkers that would be useful in early detection of this malignancy [2, 3, unpublished data]. Our panel of three protein biomarkers (REG1B, LYVE1 and TFF1) that shows promise in differentiating healthy, benign and cancer patients' groups [2] was recently further validated using additional urine samples confirming the previous results (Figure 1).

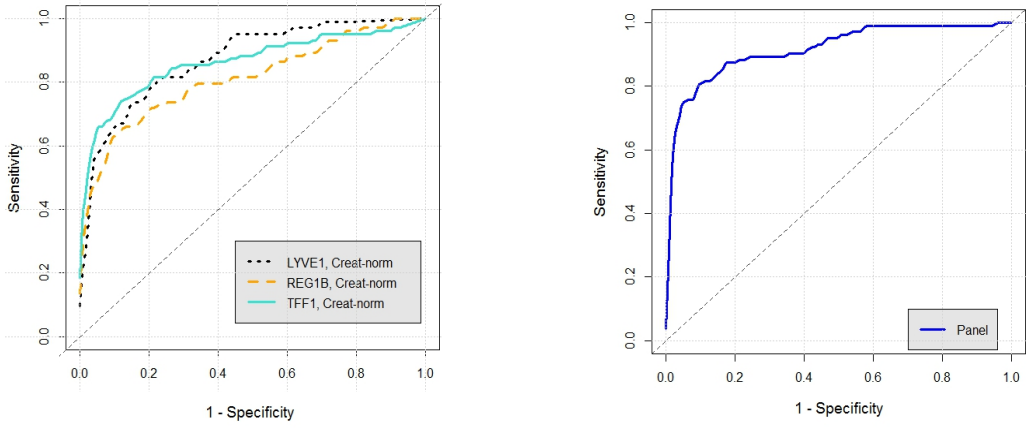

Figure 1 | Performance of urine biomarker panel in discriminating early patients with pancreatic cancer from healthy individuals: Receiver Operating Characteristic (ROC) curves of resectable stage I-II pancreatic cancer (n=103) versus healthy individuals (n=137) with AUC 0.92 (95% CI 0.88-0.95), sensitivity 80.6% (95% CI 72.8-87.4) and specificity 91.3 (95% CI 85.7-96.0).

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Rat detrusor muscle and vas deferens reactivity are negatively affected by diclofenac and indomethacin

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ABSTRACT

Introduction: Prostaglandins (PGs) and thromboxanes (TXAs) are locally acting hormones derived from arachidonic acid by the action of cyclooxygenase (COX) enzyme which exists in two distinctive isoforms, COX-1 and COX-2 (Smith, 1992). PGs have an important role in genitourinary tract function and disorders. Non-steroidal anti-inflammatory drugs are an important and efficacious class of drugs for the management of inflammatory conditions and they cause both beneficial and adverse effects via inhibition of the COX enzyme and subsequent inhibition of prostanoid synthesis (Crofford, 2013). Aim of the study: The study targets to screen the potential negative effect of COX inhibitors giving evidence about the differential sensitivity of urinary bladder, vas deferens and corpus cavernosum, and which tissue will be at lower doses. Contribution of knowledge in this field aims to enhance quality of life and reduce side effects and disease prevalence among different populations. Methods: Male Wistar rats (6-9 per group) were dissected and isolated bladder detrusor muscle, prostatic vas deferens and corpus cavernosum were used for electrophysiological organ bath chamber studies. COX-inhibitors were selected based on their COX1/COX2 selectivity (see Fig.1). All international and institutional guidelines for animal care and use were strictly followed. Results: Indomethacin, diclofenac and ketoprofen (20, 50, 100 μM) caused dose-dependent inhibition of both ACh and electric stimulation (ES)- induced contractility of detrusor muscle. EC50 of diclofenac was higher than that of indomethacin and ketoprofen. In vas deferens, indomethacin and diclofenac but not ketoprofen significantly shifted PE and ESresponse curves downwards at dose equal or higher than 50 μM. The basal contractile tone of corpus cavernosum was significantly increased by indomethacin and ketoprofen, an effect that was blocked in presence of TXA2 receptor blocker GR32191B. Indomethacin, diclofenac and ketoprofen significantly potentiated ES and ACh-induced relaxation or corpus cavernosum. SNP-induced relaxation was potentiated only in the presence of diclofenac. DFU (10^{-7}-10^{-5} M) did not show any significant effect on detrusor muscle and corpus cavernosum, however, it significantly potentiated PE-induced contractions of vas deferens. Conclusions: Diclofenac which possesses other COX- independent actions (such as LOX and TXA receptors inhibition and NO activation) showed the worst effect on bladder and vas deferens reactivity. Diclofenac and the highest selective COX-1 inhibitor, indomethacin are not recommended in bladder dysfunction and delayed ejaculatory problems. More COX-2 inhibitors seem to be devoid of this side effects but may precipitate premature ejaculation. Among the tissues tested, bladder detrusor muscle seems to be the most sensitive to the deleterious effect of nonselective anti-inflammatory drugs. COX-1 inhibition seems to enhance NO synthesis in corpus cavernosum but give upper hand to contractant PGs.

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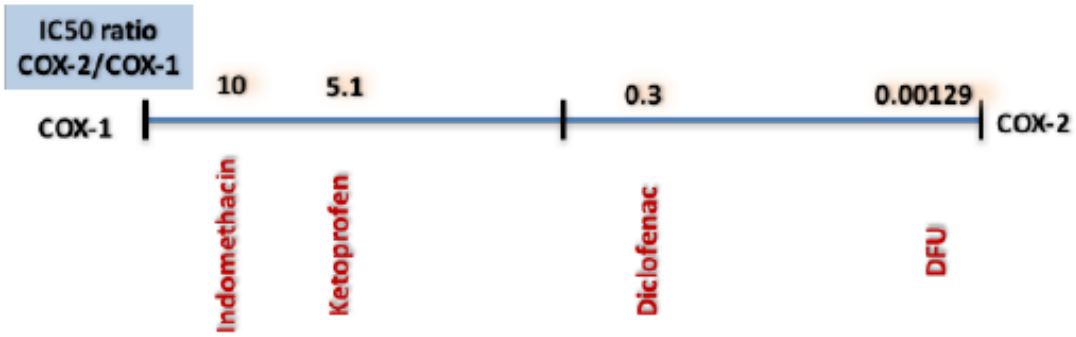

Figure 1 | (Different selectivity of chosen COX-inhibitors)

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Computer-based piRNA-mediated potential biomarker prediction in renal cell carcinoma

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ABSTRACT

Renal Cell Carcinoma (RCCa) is the 9th most common type of cancer worldwide. Like other cancers, RCCa forms as a consequence of the accumulation of many genetic and epigenetic changes. Piwi interacting RNA (piRNA) is the largest class of small non-coding RNA molecules in animal cells. piRNA-protein complexes are associated with epigenetic and post-transcriptional gene silencing. Deregulation of some piRNAs has been observed in RCCa. Some genes (*VHL, ITPR1, PPAR, GPD1L, ABHD5, IMPDH2, CHDH, DRR1, PDHB and FHIT*) on the short arm of chromosome 3 are frequently deleted in RCCa cases [1]. Four piRNAs targeting at least four of these genes were determined using piRNAdb and piRNAQuest databases. The genes (*CALN1, ELAVL1, IL1RAPL1, PARK2, WWOX*) targeted by all of these piRNAs and showing the most potential competing endogenous RNA (ceRNA) activity were detected by piRNAdbdatabase (Figure 1). These piRNAs now regulate these five ceRNAs instead of deleted genes on chr.3 in RCCa. Previous studies showed *ELAVL1* is upregulated, and *PARK2* and *WWOX* are downregulated in RCCa so these findings make this in silico analysis logical [2-4]. Up to date, no association of *CALN1* and *IL1RAPL1* with RCCa in literature makes them as potential novel biomarkers in RCCa.

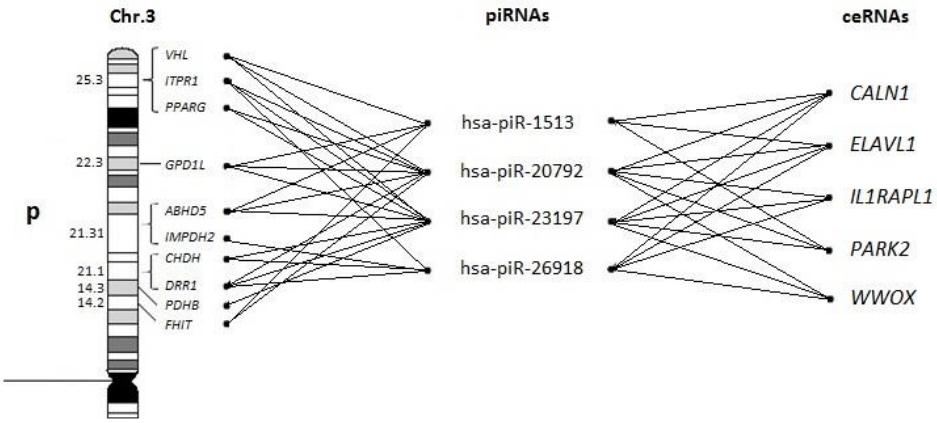

Figure 1 | In silico chromosome 3 deletions directed, piRNA-based ceRNA analysis in RCCa.

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Three approaches for studying urinary cell free DNA in urological and non-urological cancers: integrity, copy number and mutations analyses

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ABSTRACT

The role of circulating cell free DNA in cancer has already been widely demonstrated, however, less is known about the role of urine cell free DNA (UcfDNA) [1]. UcfDNA can serve as a "liquid biopsy" for urological and non-urological tumors, as it carries information on DNA from both cells exfoliated in urine and circulation [2]. Recent studies showed that cancer-related mutations may be detectable in urine specimens, plasma and tissues samples from the same patients, for both urological and non -urological diseases [3;4], indicating that UcfDNA could provide a real-time picture of the disease without the need of invasive techniques. In the present oral presentation we will focus on three different molecular approaches to detect and monitor bladder, prostate, colon and non small cell lung (NSCL) cancers. In particular, we have tested UcfDNA integrity as a diagnostic marker for bladder cancer; *c-MYC* copy number variation for prostate cancer prognosis; *KRAS* and *BRAF* mutations for colon cancer and NSCLC in comparison with tissue and plasma results. Different DNA isolation procedures were tested starting from various urine volumes and a quality assessment of DNA was proposed using bioanalyzer High Sensitivity DNA kit. Real Time PCR approaches were used to analyze integrity of three different regions of interest (*c-MYC, BCAS1, HER2*), copy number variation of *c-MYC* gene, and *KRAS* and *BRAF* mutations. We generally obtained the same DNA quality and quantity for both cancer patients and healthy individuals. Urine cell free DNA integrity showed a sensitivity of 0.73 in detecting non muscle invasive bladder cancer patients, and a specificity of 0.83 in symptomatic patients [5]. *C-MYC* copy number gain was detected in about 25% of prostate cancer patients before prostatectomy and no copy number gain was detected in healthy individuals. Regarding mutations analysis we found a concordance of 70% between tissue, plasma and urine samples. We believe that UcfDNA will have an important role in cancer diagnosis, prognosis and monitoring for bladder, prostate and non-urological tumors. However, we observed a good Real Time PCR feasibility also for non cancer patients, suggesting that these approaches could be useful also for other disease types. The analysis of nucleic acids from different body fluids should be the real goal for a personalized medicine approach, allowing the detection of informative alterations for tracking disease course.

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Levels of urinary NGAL in resistant hypertension

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ABSTRACT

Abstract. The purpose of our study was to investigate the importance of urinary neutrophil gelatinase-associated lipocalin (NGAL) in patients with resistant hypertension (RHp). A chemiluminescent microparticle immunoassay (CMIA) method became commercially available, using the automated platform ARCHITECT (Abbott Diagnostics) 1 for the measurement of NGAL in urine samples of RHp (33 with estimating glomerular filtration rate (eGFR)>60 and 17 with eGFR<60 mL/min per 1.73 m2, uNGAL–reference interval <132 μg/L)2.The incidence of chronic kidney disease was determing using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in eGFR. The study protocol complies with the Declaration of Helsinki, and was approved by the local ethics committees. Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage using the Statistics for Windows program. To investigate the relation between urinary NGAL with renal function parameters data were also stratified in groups of eGFR and information of acute kidney injury (AKI) in the past. Statistical analysis was performed by statistical package STATA/IC ver.11.1. 60.6% of RHp have eGFR >60 ml/min/1.73m2, while a 39.4% of patients have eGFR <60 ml/min/1.73m2. Levels of uNGAL were 67,91 (6,4-415,5) ug/L in RHp with eGFR<60 and 85,69 (5.1-509.9) ug/L in RHp with eGFR≥60ml/ min per 1.73 m2. There were no significant differences between levels of uNGAL and eGFR values in patients with RH (p=0.192).

Levels of uNGAL and AKI in the past were 145.2 (36.1-501.9) ug/L in 8 RHp with eGFR<60 ml/min per 1.73 m2 and 197.4 (26.2 -509.9) ug/L in 3 RHp with eGFR≥60 mL/min per 1.73 m2 (uNGAL – reference interval <132 μg/L). Higher value of uNGAL in some RHp could have link in the repair stage after AKI and would reveal pathways that could link AKI and CKD in the future.

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The Shrunken Pore Syndrome: Proteomics for further studies

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ABSTRACT

The recently described "Shrunken pore syndrome" (SPS) is characterized by a difference in glomerular filtration rate (GFR) between cystatin C and creatinine. The Shrunken pore syndrome, defined as an estimated $GFR_{cystatin}$ C less than 60% of their $eGFR_{creatinine}$, is found in about 8% of the adult Swedish population and is associated with higher mortality after coronary artery bypass grafting.

Our hypothesis is that differences in permeability for small and middle molecules indicate an early damage in the vessels of the kidneys and may be a common pathophysiological mechanism for damages in the heart and kidneys. We also investigated individuals hospitalized for the diagnosis of heart failure and found significant associations with measurements of right ventricular (RV) systolic function; (TAPSE and RV S´) (according to the equation pair CKD-$EPI_{cystatin}$ C and CKD-$EPI_{creatinine}$). We will use proteomic techniques with aptamers to study the whole human plasma proteome in relation to GFR estimated from iohexol clearance in 700 patients. GFR ranges from 8-119 mL/min/1.73 m2 and the aptamer technique has the capacity to determine 2900 proteins. Preliminary we can show differences in filtration for not only creatinine and cystatin C in these patients but also for beta trace protein. These studies will give new insight into the relation between levels of plasma proteins and GFR.

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Prostasin, the epithelial sodium channel activator, in urine of hypertensive patients and healthy subjects: relationship with aldosterone and ENaC function

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ABSTRACT

Prostasin is a serine endoprotease that is glycosylphosphatidylinositol (GPI)-anchored to the surface of epithelial cells and that is released in urine. This protease is involved in the epithelial Na channel activation [1] and a direct association between urinary prostasin concentration and the activation of the aldosterone-driven pathway has been suggested by *in vitro* and *in vivo* studies [2]. Studies in humans are few but they only could give clinical information about the relationship between prostasin, aldosterone and ENaC function. Studies on hypertensive patients are particularly informative, especially in the case of secondary forms characterised by excessive aldosterone excretion. Prostasin has, in fact, being suggested as a surrogate marker of aldosterone-dependent ENaC activity. We investigated u-prostasin concentrations in patients with primary aldosteronism, in patients with essential hypertension and in healthy subjects, to explore the correlation between prostasin and aldosterone. Methods: A total of 118 patients (62 primary aldosteronism, 56 essential hypertension patients) and 43 healthy subjects were enrolled. Biochemical and hormonal parameters were measured by applying routine laboratory methods, u-prostasin levels were assessed by ELISA and exosome prostasin levels by western immunoblotting. Results: Urinary prostasin was detectable and measurable in all samples. We could detect prostasin also in urinary exosomes. In healthy subjects urinary prostasin was similarly present in both genders, and it was not affected by the hormonal different phases of the menses. Prostasin was modulated by urinary Na, and prostasin levels appeared to be correlated with the aldosterone-to-renin ratio (ARR). Primary aldosteronism patients had higher u-prostasin levels than did essential hypertension patients. Prostasin levels were positively correlated with the ARR and inversely correlated with plasma K and urinary Na levels. Prostasin levels in the highest concentration quartile were associated with a several-fold higher probability of primary aldosteronism diagnosis in hypertensive patients,. Prostasin was specific but poorly sensitive as a diagnostic marker for primary aldosteronism by ROC curve analysis. Conclusions: Our data show that an elevated urinary prostasin concentration in humans is a specific marker for primary aldosteronism, confirming the involvement of the classical model of epithelial Na channel activation

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