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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Biological Chemistry
ESPS manuscript NO: 20111
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Science editor: Fang-Fang Ji
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[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is a great and nicely-written review. Here are my conceptual and editorial suggestions to improve it: Page 3 1st line: ECF is commonly used to abbreviate extracellular fluid, not extracellular compartments. Page 1: "kidney reabsorb the exact amount of sodium (around 24900 mM)" – is this exact or around? Re-wording is needed. Page 3 states that 25% Na+ is reabsorbed by cTAL, whereas Page 4 (1.1) says that 25% is reabsorbed in TAL. Since the second is more accurate, please correct. Page 4 There is little evidence that ClC-Ka plays a role in Cl- reabsorption. In fact, mouse knockout studies demonstrated only NDI with normal electrolyte balance and ClC-Ka (ClC-K1 in rodents) seems to be expressed chiefly in the medulla (PMID: 11143973). Page 5 second paragraph: Gitelman syndrome is actually associated with Mg2+ wasting (not retention) and patients develop hypomagnesemia. Please also provide references for the paragraph. Page 5 (1.3.1) While indeed studies 7 and 8 showed that CCD have no Na+ reabsorption and K+ secretion at the baseline (besides, S. Wall's group also reported a similar observation), this does not necessary mean that these segments do not possess transport in intact kidney. Multiple patch clamp studies demonstrated

abundant functional expression of both ROMK and ENaC on the apical membrane. In addition, this section should also describe PHA type 1 pathology in humans associated with loss-of-function ENaC, low blood pressure (at least in children), urinary Na wasting and hyperkalemia. Page 6 (1.3.2) "Moreover, they are the only cells reabsorbing Cl- in the distal nephron". As distal nephron was defined starting from cTAL, this statement is not accurate. Both cTAL and DCT cells reabsorb Cl-. Page 6 (2). I am just curious why the authors decided to include ET1 signaling to "classical" pathways, whereas purinergic signaling was considered as a "novel" pathway. The initial evidence for both pathways controlling Na+ transport appeared approximately at the same time (if I am not mistaken at the beginning of 90ies). Page 7 (2.1) in addition to AC6, other AC isoforms (most notably AC3, see PMID: 19955190) regulate water transport in the CD as well. Page 8 (2.1.2, first sentence) It is worth mentioning that this is circulating RAS. Same paragraph, last sentence: better referencing is required (for example 21339086, or other similar reviews from Navar's group). Page 9 (second line): "AT1 activation of ENaC was not obtained by calcium signaling but by activating…" sounds awkward, rewording is required. Page 9 (second paragraph) "This activation is necessary for the pressure effect of AngII". It is not clear what the authors meant by the statement. Page 9 (third paragraph). It needs to be moved in the front of 2.1.2 (the current position is awkward). Page 9 (2.1.3 and below). Starting from (40), all the remaining references appear in superscript, please make them consistent throughout the manuscript. Page 12 (first paragraph). Kallikrein needs to be defined (I mean that it is a serine protease). Page 12 (third paragraph), as a direct action of kallikrein on ENaC function was not directly demonstrated, I suggest to temper the conclusion. Page 12 (second paragraph from the bottom). The conclusion that KKS would increase ENaC-mediated reabsorption does not fit well with development of salt-sensitive reabsorption upon deletion of any of the KKS component. Instead, genetic deletion of bradykinin receptor was demonstrated to increase ENaC activity in a salt-sensitive manner (PMID:2303337). Alternatively, KKS is known to be strongly upregulated by high dietary K+ intake. Therefore, by increasing fluid delivery to CNT/CCD and by inhibiting ENaC, augmented KKS permits K+ transport (via flow-induced K+ secretion) and do not cause Na+ retention overall promoting kaliuresis. Page 13 (second paragraph) There is no evidence that AT1 coupled to Gq/11 in the CNT/CCD as it cannot increase [Ca2+]i. P

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[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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		[Y] No	

COMMENTS TO AUTHORS

To the authors: The authors review the current literature on GPCR signaling in sodium transport in the kidney. While many of the topics are reviewed elsewhere, this review is more comprehensive than those already in existence and will therefore be useful to those wanting a broad outline of the field. I read the already good article with the intent of clarifying some points and catching whatever small errors I could find. 1) In the section on purinergic regulation of ENaC, the authors mention that PLC-mediated hydrolysis of PIP2 is responsible for ENaC inhibition by P2Y2 receptors and that intracellular calcium increases have no effect. While it is known that the effects of this receptor are mediated by PLC, I believe that the current opinion is that both PLC hydrolysis of PIP2 and increases in intracellular Ca work together to inhibit ENaC. For a very good review on calcium's effect on ENaC downstream of ATP, see this article: Wildman SS, Kang ES-K, King BF. ENaC, renal sodium excretion and extracellular ATP. Purinergic Signalling. 2009;5(4):481-489. doi:10.1007/s11302-009-9150-6. My understanding of P2Y2 mediated signaling is the following: ATP is released through cx30 hemichannels following bending of primary cilia and activation of

TRPV4 channels at the base of the cilium. The subsequent localized increase in Ca activates the release of ATP. ATP binds to P2Y2 channels on the apical membrane which are Gq coupled. The Gq activates PLC which hydrolyzes PIP2 to make IP3 and DAG. The decreased level of PIP2 in the membrane would cause ENaC to drop out of the membrane, but ENaC is also inhibited in other ways by PLC. The IP3 causes release of ER Ca which may or may not have a direct inhibitory effect on ENaC (this was shown by Palmer to have no effect and by Gu to have an effect—since Palmer's experiments were in a rat tubule and not cultured cells, I am inclined to have more faith in his work, but the verdict is still officially out). In any case, there is no doubt that Ca can inhibit ENaC indirectly and that this does happen downstream of P2Y2 receptors. Even with lower PIP2, ENaC can still be somewhat active since MARCKS functions to help recruit ENaC to the remaining PIP2s in the membrane. Ca can inhibit MARCKS in two ways, first by binding to CaM and binding to the CaM binding site on MARCKS and second by working with DAG to activate PKC which phosphorylates MARCKS, causing removal from the membrane. Without MARCKS recruitment, ENaC is lost from the remaining PIP2. Ca also activates Nedd4-2, a Ub ligase known to act on ENaC. 2) The authors mention that there is no ENaC activity on a normal diet. If this is true, then why do studies on isolated split open tubules from WT mice on normal chow routinely find low but present activity of the channel? If the authors mean a normal human western diet which is high in salt, this should be noted. 3) There are several errors in formatting. For example, in figure 5, alkalosis is misspelled (maybe this is a European spelling that I am not familiar with. If so, disregard). There is a random gray highlight in section 2.1.2. The formatting of ion names is inconsistent (ie sodium vs Na+). There is a change in reference format to superscript halfway through. 4) It would help to add two more sections to the table: one saying what cell types the receptors are expressed in and one saying whether they are apical or basolaterally expressed. 5) Section 2.1.1 mentions Nedd as a regulator. It would be helpful to point out that it is not a kinase but a ub ligase (this is not clear since kinases were mentioned in the previous sentence). 6) In section 2.1.2, the distinction between tubular vs systemic RAAS is not clear and might not be understood by a reader unfamiliar with the pathways. 7) Section 2.1.3 needs more references in the introduction. 8) The alpha adrenoreceptor section mentions NO production is induced in endothelial cells but does not say how this affects

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COMMENTS TO AUTHORS

Good article