

High salt diet and caffeine: food for thought

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The popularity of coffee and other caffeine-containing beverages in the Western diet undoubtedly draws attention of researchers to the studies of caffeine-mediated effects on human physiology and disease. Another hallmark of the modern diet is high salt consumption, which is associated with cardiovascular complications. A recent research article by Yu *et al.* targets both topics and is focused on the chronic effects of caffeine consumption on the development of salt-sensitive (SS) hypertension (1). This type of hypertension is widespread, and particularly in hypertensive African American population its prevalence reaches almost 73% (2). This is a nice study targeting identification of sodium channels or transporters affected by caffeine; however, it is not the first one. For instance, Fenton *et al.* recently reported that caffeine-induced diuresis and natriuresis are independent of phosphorylation or expression of Na⁺/H⁺ exchanger isoform 3 (NHE3) in the kidney (3). Nevertheless, this manuscript is very timely and well done. The central hypothesis of the manuscript is that enhanced sodium reabsorption via the epithelial sodium channel (ENaC) that occurs in the distal nephron (4) may be decreased by chronic caffeine intake, and leads to a reduction in systolic blood pressure. This study raises a number of questions that may provoke an exciting discussion in the literature.

A well-established model of hypertension, the Dahl SS rat, was used in this study; the authors employed a panel of modern experimental approaches to characterize key cardiorenal functions in this strain. Radiotelemetry revealed that control SS rats when switched to an 8% NaCl diet for 15 days exhibit an increase in blood pressure (BP, systolic: from ~120 to 145 mmHg; diastolic from ~82 to 105 mmHg). Chronic caffeine administration [0.1% in drinking water;

a rather high amount for a rat (2.5 g/day) taking into consideration that humans consume on average 200 mg/day, up to 400 mg/day in extreme cases (5)] prevented the salt-induced raise of systolic BP, whereas diastolic BP remained unchanged. A recent clinical study showed, on the other hand, that habitual coffee consumption is associated with both systolic and diastolic pressures being higher in a coffee-drinking cohort of the hypertensive population compared to hypertensive subjects that do not include coffee in their diet (6).

Interestingly, the authors have demonstrated that the effect of caffeine was not associated with the sympathetic nerve activity and vascular component of BP control, and focused on the renal function. The lack of the vasculature-mediated changes is a rather intriguing observation, as caffeine has been long known to antagonize vasoconstriction via the action on adenosine receptors, among other effects on vessels. Undoubtedly, these statements require some careful investigation, and there is a need to always distinguish between long-term (habitual coffee intake, for instance) and acute responses to caffeine, which can have differential effects on various physiological parameters.

Further, the manuscript reports that caffeine increased natriuresis (but not diuresis) without affecting plasma sodium concentration, and this might have caused lower total body fluid volume and blood pressure. The authors themselves review in the introduction of the discussed manuscript that caffeine has prominent diuretic properties, and impaired diuresis is indeed an important contributor to chronic hypertension. It remains for the future investigators to reveal whether this observed absence of caffeine-induced diuresis is just pertinent to the Dahl SS rat strain, or there are more complicated mechanisms involved.

Particularly in the Dahl SS rats the decreased abundance or inhibition of renal sodium transporters (NKCC2, NCC, ENaC) are associated with lower blood pressure (7-11). The Western blot analysis of the isolated CNT/CCD segments did not reveal a difference in NCC level between the caffeine-treated and control groups. However, the data should be reviewed with caution, as the conclusion was made based on a ~40 kDa molecular weight band (as indicated in the supplementary figure) which is not typical for NCC (12-14). Similarly, the analysis of an active, phosphorylated form of NCC would have benefited this study.

A compelling set of data was collected regarding ENaC regulation by caffeine. Earlier we and others demonstrated that ENaC activity in distal nephron contributes to the development of hypertension in Dahl SS rats when animals are placed on a high salt diet (due to the persistent high expression of α -ENaC and increased abundance of β - and γ -ENaC subunits) (8,11). Yu and colleagues found that caffeine treatment significantly decreases α -ENaC abundance, and this might be the driving factor for the improved natriuresis they observe. Additional confirmation of this idea came from *in vivo* experiments which demonstrated that effect of the caffeine on natriuresis could be blocked by an ENaC inhibitor amiloride, but not by thiazide diuretics targeting NCC.

Further experiments were performed in the M1-CCD cell line which represents a model of transepithelial reabsorption in the cortical collecting ducts. Incubation with caffeine, consistent with animal tissue data, led to a dose-dependent decrease of α -ENaC (but not β - and γ -ENaC) subunit expression. In order to mechanistically characterize the observed phenomena, the authors assayed the activity of three kinases that might be involved in regulation of ENaC activity and found that caffeine did not change the abundance of SGK1, ERK1/2 or PKC α , but rather dose-dependently decreased phosphorylation and abundance of AMPK α . Earlier findings by others also revealed that AMPK activation can decrease ENaC-mediated sodium current in mouse collecting ducts and airway epithelial cell lines (15,16). The reported data is an excellent confirmation of the idea that downregulation of ENaC is beneficial during SS hypertension, and chronic caffeine consumption may be one of the factors facilitating a reduction in ENaC function and/or expression.

However, the reader should be strongly warned against the direct translation of data obtained in cell cultures to the *in vivo* environment of a Dahl SS rat. The M1-CCD

cells used by the authors or mpkCCD_{c14} cells used in (15) were derived from healthy mice (17,18); earlier studies on CCD preparations freshly isolated from normal mice demonstrated that there is no effect of caffeine on ENaC open probability (19). Dahl SS rats possess a number of aberrant physiological traits compared to salt resistant rodents, and greater caution should be exercised with the attempts to reduce a research object. As mentioned above, the Dahl SS strain shows abnormal activation of ENaC in response to a high NaCl diet (whereas salt-resistant animals exhibit decreased ENaC activity when challenged with high salt), and this situation cannot be completely reproduced in cultured cells. Additionally, the use of cultured cells unfortunately limits the ability to perform physiologically appropriate control experiments; for instance, a group exposed to a low salt diet would be essential to assess the range of the caffeine-induced changes in ENaC subunits levels. Importantly, the expression of kinases was also shown in cell culture only, and it is unclear how high salt diet challenge can change the activity of the key kinase of the manuscript—AMPK—in Dahl SS rats *in vivo*. From a previous publication we know that treatment of Dahl SS rats with metformin, an indirect AMPK activator, does not affect the development of SS hypertension (20); therefore, this question remains open.

To sum up, the discussed manuscript is very intriguing and suggests potential molecular targets for a translational approach to treatment of SS hypertension, and emphasizes the contribution of ENaC-mediated sodium reabsorption in the distal nephron to blood pressure regulation. However, further extensive studies are encouraged in order to answer the curious question: should the salt-sensitive population reduce or increase their caffeine intake?

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Footnote

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References

1. Yu H, Yang T, Gao P, et al. Caffeine intake antagonizes salt sensitive hypertension through improvement of renal sodium handling. *Sci Rep* 2016;6:25746.
2. Weinberger MH, Fineberg NS, Fineberg SE, et al. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension* 2001;37:429-32.
3. Fenton RA, Poulsen SB, de la Mora Chavez S, et al. Caffeine-induced diuresis and natriuresis is independent of renal tubular NHE3. *Am J Physiol Renal Physiol* 2015;308:F1409-20.
4. Staruschenko A. Regulation of transport in the connecting tubule and cortical collecting duct. *Compr Physiol* 2012;2:1541-84.
5. Mitchell DC, Knight CA, Hockenberry J, et al. Beverage caffeine intakes in the U.S. *Food Chem Toxicol* 2014;63:136-42.
6. Lopez-Garcia E, Orozco-Arbeláez E, Leon-Muñoz LM, et al. Habitual coffee consumption and 24-h blood pressure control in older adults with hypertension. *Clin Nutr* 2016. [Epub ahead of print].
7. Haque MZ, Ares GR, Caceres PS, et al. High salt differentially regulates surface NKCC2 expression in thick ascending limbs of Dahl salt-sensitive and salt-resistant rats. *Am J Physiol Renal Physiol* 2011;300:F1096-104.
8. Pavlov TS, Levchenko V, O'Connor PM, et al. Deficiency of renal cortical EGF increases ENaC activity and contributes to salt-sensitive hypertension. *J Am Soc Nephrol* 2013;24:1053-62.
9. Pavlov TS, Levchenko V, Ilatovskaya DV, et al. Renal sodium transport in renin-deficient Dahl salt-sensitive rats. *J Renin Angiotensin Aldosterone Syst* 2016;17. pii:1470320316653858.
10. Hoagland KM, Flasch AK, Dahly-Vernon AJ, et al. Elevated BSC-1 and ROMK expression in Dahl salt-sensitive rat kidneys. *Hypertension* 2004;43:860-5.
11. Aoi W, Niisato N, Sawabe Y, et al. Aldosterone-induced abnormal regulation of ENaC and SGK1 in Dahl salt-sensitive rat. *Biochem Biophys Res Commun* 2006;341:376-81.
12. Plotkin MD, Kaplan MR, Verlander JW, et al. Localization of the thiazide sensitive Na-Cl cotransporter, rTSC1 in the rat kidney. *Kidney Int* 1996;50:174-83.
13. Terker AS, Yarbrough B, Ferdaus MZ, et al. Direct and Indirect Mineralocorticoid Effects Determine Distal Salt Transport. *J Am Soc Nephrol* 2016;27:2436-45.
14. Gamba G, Miyanoshita A, Lombardi M, et al. Molecular cloning, primary structure, and characterization of two members of the mammalian electroneutral sodium-(potassium)-chloride cotransporter family expressed in kidney. *J Biol Chem* 1994;269:17713-22.
15. Weixel KM, Marciszyn A, Alzamora R, et al. Resveratrol inhibits the epithelial sodium channel via phosphoinositides and AMP-activated protein kinase in kidney collecting duct cells. *PLoS One* 2013;8:e78019.
16. Myerburg MM, King JD Jr, Oyster NM, et al. AMPK agonists ameliorate sodium and fluid transport and inflammation in cystic fibrosis airway epithelial cells. *Am J Respir Cell Mol Biol* 2010;42:676-84.
17. Stoos BA, Náráy-Fejes-Tóth A, Carretero OA, et al. Characterization of a mouse cortical collecting duct cell line. *Kidney Int* 1991;39:1168-75.
18. Bens M, Vallet V, Cluzeaud F, et al. Corticosteroid-dependent sodium transport in a novel immortalized mouse collecting duct principal cell line. *J Am Soc Nephrol* 1999;10:923-34.
19. Zaika O, Mamenko M, O'Neil RG, et al. Bradykinin acutely inhibits activity of the epithelial Na⁺ channel in mammalian aldosterone-sensitive distal nephron. *Am J Physiol Renal Physiol* 2011;300:F1105-15.
20. Kotchen TA, Zhang HY, Covelli M, et al. Insulin resistance and blood pressure in Dahl rats and in one-kidney, one-clip hypertensive rats. *Am J Physiol* 1991;261:E692-7.

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