In this issue of Hypertension, Jeggle et al provide important new insights into the characteristics and functional significance of an amiloride-sensitive sodium channel that is expressed in vascular endothelial cells. This work extends the previous analyses by this group, and using atomic force microscopy and state-of-the-art animal and cell models, provides provocative yet conclusive evidence for the central role of this channel in regulation vascular reactivity and stiffness.

The Figure depicts the heteromeric structure of the amiloride-sensitive sodium channel. Although the overall topology of the channel is well described, there is no general agreement about the subunit composition even within epithelial cells, much less in other tissues like vascular endothelial cells that are the subject of the current report. The bulk of the subunits’ structures are expressed in the intertwined disulfide-rich extracellular domains, the role of which has not been fully explained. The subunits of the epithelial sodium channel (ENaC) were originally defined by now-classical expression cloning studies by Canessa and Rossier. The human genomic clones and the critical insight into the gain of function effect that characterizes Liddle syndrome was based on analogy to defects in the mechanosensor structures of degenerins in Caenorhabditis elegans.

Although longitudinal flow is certainly a feature of many epithelial tubule systems, a direct connection among the putative mechanical transduction function, the extracellular domains, and regulation of apical sodium entry via ENaC is not obvious. In contrast, there are pulsatile pressures and flows in the systemic vascular system. Local regulation of vascular tone in response to changes in pressure and shear stress, an important feature of the microvascular circulation, lending credance to the idea that the extensive extracellular of the vascular endothelial sodium channel (ENaC) domain could serve as a mechanoforce transducer. Using atomic force spectroscopy and nanoindentation analysis, the current report describes the regulation of cortical stiffness through the agency of the ENaC, either related to apical sodium entry or interactions with the cortical actin cytoskeleton.

In the context of the current work, cortical stiffness is defined as the force needed to indent the individual cell cortex (eg, apical surface) for a fixed distance, and hence directly reflects the mechanical rigidity of the submembraneous region. The actin cytoskeleton is assumed to organize this subapical structure; dynamic changes in the organization and expression of the actin cytoskeleton directly regulates the submembraneous rigidity. The role of ionized calcium, nitric oxide, and other vasoactive agents like angiotensin II in regulating cortical stiffness, and the responsibility to various classes of antihypertensive medications are obvious areas for future inquiry.

An important role of aldosterone in regulating cortical stiffness, and the use of knock-down and gain-of-function cellular models strongly supports the critical role of ENaC in maintaining vascular tone at the individual endothelial cellular level. The current findings take on added relevance with the recent description of vascular endothelial mineralocorticoid receptors, and the appreciation of the importance of local renin-angiotensin-aldosterone system in regulating vascular tone. The parallel evolutionary significance of the development of α and β subunits of the sodium channel and the sodium-potassium ATPase has recently been reviewed. With elucidation of the autosomal dominant monogenic gain-of-function defect in Liddle syndrome, the phenotypic extreme of low-renin hypertension was defined, an example par excellence of the Guytonian view of maintaining salt balance and homeostasis. This view emphasizes the importance of salt intake and balance in maintaining the milieu intérieur, and also identifies systemic hypertension with resulting pressure natriuresis as the effector arm of this control loop. What has not been adequately addressed is the mechanism(s) by which dietary salt intake, aldosterone status, and vascular tone participate in the effector arm of the Guytonian servolop. The new findings reported herein by Jeggle and colleagues provide an approach to defining the effector arm at the level of individual vascular endothelial cell, whereas the overall regulation of salt balance by the classically described ENaC/Na-K-ATPase mechanisms focus at the level of whole-organ physiology.

I introduce novel, in this comment, nomenclature for the EpNaC and the EnNaC in an attempt to stimulate further discussion and experimental effort. ENaC, as a term, would seem to have use in describing the entire family of related amiloride-sensitive sodium channels (even though the E classically refers to epithelial). Although there seem to be many similarities, and both complexes are undoubtedly part of the ENaC/degenerin superfamily, there are important functional distinctions emphasized in the current work that clearly warrant additional investigations and inquiries. The time has come
and largely eliminates the Na+ self-inhibition response, which
subunit (L511Q) that increases amiloride-sensitive currents
ENaC and colleagues describes a novel point mutation in the
concentrations of 140 mmol/L. A recent report by Kleyman
by amiloride in the presence of normal extracellular sodium
reduce the effectiveness of sodium channel blockade observed
there was a striking effect of increased dietary sodium intake
fore.14 Unfortunately, the cardioprotective effects associated
vascular disease, with novel new approaches coming to the
system blockade is an important avenue for treating chronic
kidney disease and reducing mortality in cardiovascular dis-
ese. Major efforts have demonstrated the clinical benefit of
using mineralocorticoid receptor antagonism in cardio-
vascular disease, with novel new approaches coming to the
fore.14 Unfortunately, the cardioprotective effects associated
with mineralocorticoid receptor blockade nearly 15 years
ago15 are not readily available to patients with moderate-to-
severe chronic kidney disease who can develop dose-limiting
hyperkalemia in the setting of aggressive renin-angiotension-
aldosterone system blockade, such as described in the recent
ALTITUDE Trial.16
Previous consideration has been given to trying to separate
the effects of Na-channel blockers like amiloride or triam-
terene from the parallel decreases in K+ secretion that invari-
ably accompany EpNaC blockade. Furthermore, the currently
available EpNaC blockers do not have a substantial effect on
reduction of systemic blood pressure, at least in the currently
used dosing regimens.17 An exception to this overall analysis
is provided by the salutary responses to amiloride in adoles-
cents with Liddle syndrome, who presumably have not devel-
oped the long-term vascular changes associated with chronic
hypertension, although this effect may represent a primary
renal effect rather than an effect on the vascular endothelium
in Liddle syndrome and is clearly predicated on control of
dietary salt intake.9,13
ENaC may present a specific target for therapeutic inter-
vention if its inhibition can be functionally separated from
EpNaC, and thus avoiding or at least minimizing impairment
of renal and intestinal K+ secretion. Recent developments of
novel 2-acyl-amiloride derivatives18,19 may provide a poten-
tial avenue for further development. An interesting analogue
would have reasonable bioavailability (oral, sublingual, or
transdermal), with hepatobiliary rather than renal clear-
ance, and effectiveness as a noncompetitive inhibitor against
ENaC at subnanomolar concentrations. Amiloride, at usual
oral dosing, achieves plasma levels that are well below the
IC50 for ENaC, with nearly 100-fold greater concentrations
present in the final urine.20 Appropriate preclinical and clini-
cal models and trials will need to be carried out to determine
whether amiloride analogues can be developed that are renal
sparring, minimize hyperkalemia, and also provide effective
antihypertensive effects as well as longer term cardioprotec-
tive effects such has been described with mineralocorticoid
receptor blockade.

Sources of Funding
Preparation of this comment was supported by the Hilda B. Anderson
Endowed Chair in Nephrology at the University of Alabama at
Birmingham.

Disclosures
D.G. Warnock serves as a consultant to Parion Sciences Inc and
Gilhead Sciences Inc on the clinical development of amiloride
analogues.

References
Kusche-Vihrog K. Epithelial sodium channel stiffens the vascular endo-
2. Kusche-Vihrog K, Sobczak K, Bangel N, Wilhelmi M, Nechyporuk-
Zloy V, Schwab A, Schillers H, Oberleithner H. Aldosterone and
amiloride alter ENaC abundance in vascular endothelium. Pflugers Arch.
3. Fels J, Oberleithner H, Kusche-Vihrog K. Ménage à trois: aldosterone,
sodium and nitric oxide in vascular endothelium. Biochim Biophys Acta.


The Amiloride-Sensitive Endothelial Sodium Channel and Vascular Tone

David G. Warnock

Hypertension. 2013;61:952-954; originally published online March 4, 2013; doi: 10.1161/HYPERTENSIONAHA.113.00768

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/61/5/952

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/