Role of Epithelial Sodium Channels in the Renal Myogenic Response?

To the Editor:

The recent publication by Guan et al.¹ and the accompanying editorial in a recent issue of *Hypertension*² both state that the findings of Guan et al.¹ contradict the observations that we published previously concerning the effects of benzamil and amiloride on the myogenic response of the renal afferent arteriole.³ We argue that much of the data in the 2 studies are, in fact, complementary. In Guan et al.¹ and in our study, benzamil and amiloride did not inhibit the afferent arteriolar myogenic response at concentrations ≤1 μmol/L. We observed no effect of 3 μmol/L of amiloride, whereas Guan et al.¹ found 5 μmol/L of amiloride to fully block myogenic responses. It is important to note that the original studies implicating epithelial sodium channels (ENaCs) in myogenic signaling reported inhibition at 10 nmol/L. Studies directly evaluating the blockade of ENaC reported full inhibition. It is important to note that the original studies implicating epithelial sodium channels (ENaCs) in myogenic signaling reported inhibition at 10 nmol/L. Studies directly evaluating the blockade of ENaC reported full inhibition.

The specificity of pharmacological probes invariably depends on concentration. This is particularly true of amiloride and its derivatives. These agents inhibit ENaC at submicromolar concentrations. Higher levels affect nearly all of the sodium transporters and alter the function of a wide variety of ion channels and enzymes (reviewed in Reference³). Benzamil blocks ENaC with an IC₅₀ of ≈10 nmol/L (~10 times lower than that of amiloride⁴) and the Na⁺/Ca²⁺ exchanger with an IC₅₀ of 100 nmol/L. Studies directly evaluating the blockade of ENaC currents routinely demonstrate that 1 μmol/L of amiloride and benzamil block ENaC by ~80% and 90% to 100%, respectively. Accordingly, we interpret the observations made by both our laboratory³ and Guan et al.¹ that, at 1 μmol/L, neither benzamil nor amiloride inhibits the myogenic response of the afferent arteriole as suggesting that ENaC plays little if any role in myogenic signaling in this vessel.

On observing no effects at 1 μmol/L, Guan et al.¹ examined the effects of 10 μmol/L of benzamil and observed full inhibition. They interpreted this action as being attributed to ENaC blockade. The comprehensive review by Kleyman and Crangoe,⁵ written >2 decades ago, strongly warns against such interpretations, emphasizing the broad range of protein functions altered by amiloride analogues at such concentrations. We also observed marked effects of 10 μmol/L of benzamil on the afferent arteriole, but these actions were clearly not related to ENaC blockade (see Reference³ for discussion). Thus, our observations and those of Guan et al.¹ are quite similar. It is only our interpretations of these data that differ.

Finally, we could not consistently detect α, β, or γ ENaC mRNA in afferent arterioles.³ Using immunofluorescence, Guan et al.¹ report all 3 of the subunits to be expressed. Although the reasons underlying these apparently incompatible results await further investigation, it is noteworthy that the presence of the α subunit is suggested by Drummond et al.⁴ to be incompatible with a role for the protein complex in mechanotransduction, because a constitutively active channel should be present if all 3 of the subunits are expressed. Direct electrophysiological approaches may ultimately resolve this issue and determine whether a channel with the functional and pharmacological properties of ENaC is observed in afferent arteriolar myocytes.

Disclosures

None.

Rodger Loutzenisher
Smooth Muscle Research Group
University of Calgary Faculty of Medicine
Calgary, Alberta, Canada

Philip I. Aaronson
Division of Asthma, Allergy, and Lung Biology
King’s College London
London, United Kingdom

Role of Epithelial Sodium Channels in the Renal Myogenic Response?
Rodger Loutzenhiser and Philip I. Aaronson

Hypertension. 2010;55:e6; originally published online December 28, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.147132

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/55/2/e6

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/