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See related articles, "Race, Gender, and Socioeconomic Disparities in CKD in the United States," on pages 1261–1270, and "Let's Get Serious About Racial and Ethnic Disparities," on pages 1271–1275.

Glucocorticoid-Mediated Hypertension: Does the Vascular Smooth Muscle Hold All the Answers?

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Patients treated with glucocorticoids for a variety of diverse diseases and those with Cushing syndrome often manifest hypertension. Despite the importance of this clinically relevant problem, the mechanism whereby glucocorticoids increase BP remains an enigma. Although it may be logical to reason that glucocorticoids increase renal salt absorption, resulting in an expansion of the extracellular fluid volume and hypertension, this rationale is not supported by data. Glucocorticoids do not affect serum potassium levels and urinary sodium, and potas-

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sium excretion is either unaffected[1,2] or increased despite an increase in BP.[2–5] Furthermore, spironolactone does not affect the BP in patients with Cushing syndrome or adrenocorticotrophic hormone (ACTH)-induced hypertension in rats, indicating that promiscuous activation of distal tubule mineralocorticoid receptor by glucocorticoids does not play a role in glucocorticoid-mediated hypertension.[5,6]

Numerous studies have provided indirect evidence that the increase in BP mediated by dexamethasone, a glucocorticoid without mineralocorticoid activity, is due to an increase in systemic vascular resistance. Peripheral vascular resistance is a balance between the effect of vasoconstrictors and vasodilators, and both arms have been shown to be regulated by glucocorticoids. Using intravital microscopy to measure the arteriolar diameter in mice *in vivo*, dexamethasone attenuated the vasodilatory response to acetylcholine.[1]

Endothelial nitric oxide (NO) is an important physiologic vasodilator generated by endothelial NO synthetase III.[1,7] Administration of glucocorticoids to mice resulted in a decrease in the serum NO metabolites NO_2^- and NO_3^-, an indirect indicator of serum NO levels, and a reduction in endothelial NO synthase III mRNA abundance in aorta, liver, and kidney as a result of decreased transcription and increased degradation.[1,7] Glucocorticoid- and ACTH-mediated hypertension in rats can be mitigated by L-arginine, the precursor to NO, and the L-arginine effect can be blocked by NO synthetase inhibition.[7,8] Finally, endothelial NO null mice do not develop hypertension when given dexamethasone.[9] These findings are consistent with a role for NO in mediating the hypertension by glucocorticoids.[8]

In addition to NO, a reduction in other vasodilators may play a role in glucocorticoid-mediated hypertension. Patients with Cushing syndrome have a reduction in urinary prostaglandin and kallikrein excretion.[5] Studies examining the effect of bradykinin and prostaglandin infusions on BP in dexamethasone-treated dogs are consistent with a role for prostaglandins and kallikrein-kinins in glucocorticoid-induced hypertension.[5]

There is also evidence that glucocorticoids enhance the effect of vasoconstrictors. Glucocorticoids increase rat aortic smooth muscle cell angiotensin II (AngII) receptor IA mRNA and protein abundance by increasing AngII receptor IA promoter activity.[10] Blockade of the renin-angiotensin system attenuates the glucocorticoid-mediated rise in BP.[11,12] Both AngII and norepinephrine infusion produce a greater increase in diastolic BP in patients with Cushing syndrome than in normal individuals.[5] The pressor response to norepinephrine is enhanced in glucocorticoid-treated compared with control rats.[4] Thus, circulating AngII and catecholamines may have a more profound effect on BP with elevated levels of glucocorticoids.

The literature indicates that the causes for the increase in BP by glucocorticoids is multifactorial, but all indirectly incriminate increasing peripheral vascular resistance as a principal mechanism; however, these studies are indirect and do not exclude other possibilities to explain the rise in BP induced by glucocorticoids. In this issue, Goodwin *et al.*[13] took a more direct approach to study the pathogenesis of glucocorticoid-mediated hypertension. They selectively deleted the glucocorticoid receptor from vascular smooth muscle in mice (Sm-GC knockout mice). The control and the knockout mice had similar basal and circadian variations in BP. Dexamethasone administration resulted in an increase in BP within the first day in control mice but not in the Sm-GC knockout mice, consistent with an important role of the glucocorticoid receptor in the vascular smooth muscle mediating the acute response to glucocorticoids. Although the rise in BP was attenuated in the knockout mice, they developed a delayed but significant increase in BP with dexamethasone over the baseline measurements.

This study demonstrates the importance of the glucocorticoid receptor in the arteriolar smooth muscle cells in the acute generation of hypertension by glucocorticoids[13]; however, this study points out that there is still a lot that we do not understand about glucocorticoid-mediated hypertension and a lot we can learn from future studies of these Sm-GC knockout mice. It would be of interest to examine whether there is an attenuated response to vasodilators and increased response to norepinephrine and AngII in dexamethasone-treated Sm-GC knockout mice compared with control. Most important, the Sm-GC knockout mice developed an increase in BP with time with dexamethasone treatment that must be explained. Clearly, other glucocorticoid receptors besides that in smooth muscle must be involved in mediating the increase in BP in Sm-GC knockout mice with dexamethasone treatment.

Previous studies have shown that glucocorticoids increase cardiac output,[14] but this increase was not believed to play a major role in mediating the increase in BP in humans. This will need to be reexamined in future studies using these Sm-GC knockout mice and mice with selective deletion of the cardiac glucocorticoid receptor. Interestingly, the Sm-GC knockout mice had an increase in cardiac glucocorticoid receptor abundance compared with control. This may be a compensatory factor that may play a role in the delayed dexamethasone-mediated hypertension in the Sm-GC knockout mice. Furthermore, the vascular endothelium has glucocorticoid receptors that play a role in regulating NO production, which affects the glucocorticoid-mediated increase in BP.[1,7–9]

Both the Sm-GC knockout and control mice had an acute increase in sodium excretion with dexamethasone administration. Because there was no acute increase in BP with dexamethasone in Sm-GC knockout mice, this is likely not a pressure natriuresis. Glucocorticoids increase both GFR[15] and proximal tubule sodium absorption.[16] It is possible that the glucocorticoid-mediated increase in GFR occurred before the increase in tubular reabsorption, resulting in glomerular tubular imbalance and a natriuresis, a hypothesis testable in this novel Sm-GC knockout mouse. It is curious that the 43 to 87% increase in sodium excretion in the two groups of animals was not accompanied by changes in chloride or decrease potassium excretion, leaving the possibilities of steroid-induced phos-

phaturia[17,18] or hitherto unknown steroid-induced bicarbonaturia. If this is indeed sodium phosphaturia, then it will not be relevant to extracellular fluid volume or BP homeostasis.

In summary, Goodwin *et al.*[13] provide a convincing animal model of a common clinical condition that will be valuable for a host of further pathophysiologic studies.

DISCLOSURES

None.

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See related article, "A Critical Role for Vascular Smooth Muscle in Acute Glucocorticoid-Induced Hypertension," on pages 1291–1299.

Marconi Revisited: From Kidney to Brain—Two Organ Systems Communicating at Long Distance

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In this issue of *JASN*, Liu *et al.*[1] demonstrate in an animal model that acute kidney injury (AKI) is related to anatomic lesions and functional disturbances of the brain. This connection seems linked in part to inflammation. Inflammatory markers are increased after AKI not only in serum and kidneys but also in brain. Such long-distance interorgan cross-talk is observed for heart and lungs[2–4] as a result of the release of humoral factors generated in damaged kidneys that seep into blood. In the case of the brain, however, the mechanism might be more complex, because the brain-blood barrier (BBB) normally interferes with trespassing substances.

The existence of a link between inflammation and the brain has been suggested previously regarding development of fever and so-called "sick behavior."[5] The brain lesions observed after AKI[1] seem more severe and more definitive (with pyknosis and cell death) *versus* what is observed in mere sick behavior. Probably damage to the kidney triggers more profound mechanisms because a vital organ is affected and a larger number of messengers are released. Uremic encephalopathy in AKI usually presents in a dramatic way with a fast progression from mild sensorial clouding to delirium and coma.[6]

How is it possible that distant inflammation affects the brain? Several different mechanisms are possible[5,7]: Cytokines

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