Stiff Endothelial Cell Syndrome in Vascular Inflammation and Mineralocorticoid Excess

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The hypertensive effect of mineralocorticoid excess or hyperaldosteronism has traditionally been attributed to upregulation of the epithelial Na⁺ channel ENaC in the kidney, with subsequent renal salt retention, increased plasma volume, augmented cardiac filling, and thus enhanced cardiac output. The effects of extracellular volume expansion and volume, augmented cardiac filling, and thus enhanced cardiac output on blood pressure at any given peripheral resistance remain unabated. However, within the past years, it became obvious that aldosterone exerts a variety of effects in vascular cells, which may contribute to its hypertensive action and the pathophysiological consequences of mineralocorticoid excess. Notably, mineralocorticoid excess is associated with vascular inflammation. Moreover, mineralocorticoids stimulate fibrosis of cardiac and renal tissue. Aldosterone stimulates the formation of the serum and glucocorticoid-inducible kinase SGK1, which, in turn, phosphorylates multisubunit IκB kinase, eventually leading to activation of the nuclear factor κB. The transcription factor triggers the expression of a variety of genes, including connective tissue growth factor CTGF. Lack of SGK1 largely abrogates the fibrosing effect in heart and kidney of mineralocorticoid and salt excess. The fibrosing effect of mineralocorticoids is not simply the result of hypertension because before renal fibrosis, blood pressure increases to similarly high levels in SGK1 knockout mice and wild-type mice, but only the wild-type mice develop fibrosis. SGK1-dependent nuclear factor κB formation is further involved in the regulation of tissue factor synthesis and thus the stimulation of coagulation. In addition, aldosterone stimulates endothelial exocytosis and release of the prothrombotic von Willebrand factor.

Most recently, aldosterone has been shown to stimulate the insertion of ENaC into the cell membrane of endothelial cells, thus leading to early swelling and later stiffening of those cells. Aldosterone further augments the triggering of endothelial stiffening by Na⁺ excess. Endothelial cell stiffness counteracts the endothelial formation of nitric oxide (NO) and thus undermines the ability of endothelial cells to trigger vasodilation. Thus, stiffening of endothelial cells is expected to favor increase of blood pressure. Inhibition of ENaC has been shown to enhance NO formation through activation of phosphatidylinositol 3 kinase (PI3K)/Akt signaling.

Using immunofluorescence, Kusche-Vihrog et al now present evidence that C-reactive protein (25 mg/L) fosters the insertion of ENaC into the cell membrane of cultured endothelial cells. Using atomic force microscopy, they demonstrate that C-reactive protein (≥25 mg/L) enhances the stiffness of those cells. The effect on the stiffness was abrogated by the ENaC inhibitor amiloride (1 μmol/L) or by a 24-hour pretreatment with the mineralocorticoid receptor blocker spironolactone (5 mmol/L). Accordingly, C-reactive protein augments the effect of aldosterone on endothelial cell stiffness. In the absence of aldosterone, C-reactive protein was without appreciable effect on endothelial stiffness. The triggering of stiffness by C-reactive protein does not require supraphysiological aldosterone concentrations. The experiments in cultured endothelial cells were paralleled by similar observations in ex vivo patches of mouse aorta.

In theory, ENaC could modify cell stiffness by interaction with the cytoskeleton. However, the efficacy of amiloride is suggestive for a role of Na⁺ entry through the channel. Both endothelial stiffness and endothelial cell swelling are presumably triggered by Na⁺ entry through ENaC, with subsequent depolarization of the cell membrane as well as entry of Cl⁻ and osmotically obliged water. However, the swelling is transient, whereas the stiffness is more sustained and is paralleled by structural changes within the endothelial cell. The increase of endothelial cell stiffness after C-reactive protein exposure was paralleled by a decrease of permeability, which may in part result from tightening of the paracellular space.

The full effect of C-reactive protein on endothelial stiffness required some 20 minutes and is thus not likely attributable to genomic effects. It is tempting to speculate that aldosterone is required to upregulate the expression of ENaC or ENaC-regulating signaling molecules and that C-reactive protein fosters, together with aldosterone, the subsequent insertion of the channel into the plasma membrane.

Plasma levels of C-reactive protein are increased in inflammatory disease. Enhanced concentrations of C-reactive protein are associated with vascular lesions and are predictive of cardiovascular outcome. C-reactive protein is not only a diagnostic indicator of vascular disease but plays an active role in vascular injury after inflammation. Mechanisms linking C-reactive protein to vascular injury include inhibition of endothelial NO formation, an effect attributed to inhibition of PI3K/Akt signaling. PI3K stimulates SGK1, which is known to upregulate ENaC. It is tempting to
speculate that the PI3K inhibition is part of a negative feedback limiting the insertion of ENaC into the cell membrane.

Inflammation is accompanied by vasodilation and increase of vascular permeability, which may lead to life-threatening decrease of blood pressure in sepsis. C-Reactive protein may suppress NO release in order to counteract hypotension but, by the same token, may predispose to development of hypertension. Accordingly, endothelial stiffening and subsequent inhibition of NO release may contribute to the well-known stimulation of atherosclerosis by C-reactive protein.

The observations of Kusche-Vihrog et al disclose a novel mechanism contributing to the link between inflammation and vascular disease and highlight the role of endothelial stiffening in the pathophysiology of endothelial dysfunction. Endothelial cell stiffness is presumably an integral part of the machinery leading to hypertension during mineralocorticoid and salt excess (Figure).

Further experimental effort is needed to elucidate the physiological and pathophysiological ramifications of stiff endothelial cell syndrome. For example, it was highly interesting to learn whether the upregulation of ENaC in endothelial cells by aldosterone is accomplished by similar mechanisms as in the aldosterone-sensitive nephron segments and whether it involves SGK1-sensitive signaling. Moreover, it was interesting to learn more about the signaling between C-reactive protein and ENaC and between endothelial stiffness and NO formation. It was also interesting to explore whether other triggers of hypertension, such as angiotensin II or glucocorticoids, influence the mechanic properties of endothelial cells and whether endothelial stiffening compromises further endothelial functions, such as inhibition of coagulation or regulation of local inflammation.

Clearly, the exciting article of Kusche-Vihrog et al opens a door for novel research, eventually unraveling the role of endothelial cell stiffness in inflammatory and vascular disease. Further experimental evidence will undoubtedly identify additional clinical conditions in which stiff endothelial cell syndrome plays a decisive pathophysiological role.

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