Calcium, Magnesium, and Oxidative Stress in Hyperaldosteronism

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Hyperaldosteronism has been demonstrated to be associated with magnesium loss in the urine and hypomagnesemia as part of the syndrome of metabolic alkalosis and hypokalemia that characterizes this condition. In this issue of Circulation, Chhokar et al demonstrate the consequences of metabolic changes in rats subjected to aldosterone infusion in the presence of excess salt that result in hypocalcemia and hypomagnesemia, hyperparathyroidism, bone resorption, and calcium overload of tissues including the heart. This is associated with the enhanced production of reactive oxygen species (ROS) and an inflammatory phenotype, which then contribute to the decline in cardiac function and the progression to heart failure.

Our knowledge of the (patho)physiological role of aldosterone and that of magnesium has increased dramatically during the past few years. The finding that aldosterone acts on target tissues other than the classic epithelial cells (kidney, colon) has had a profound influence on our understanding of the significance of aldosterone in cardiovascular disease. Aldosterone is now known to act on the heart and blood vessels, not only on muscle (smooth muscle and cardiomyocytes), but also on endothelial cells, where it induces nuclear swelling, which has been implicated in the mechanisms of vascular damage. Part of the effects of aldosterone may be mediated by the upregulation of endothelin-1 gene expression in the vasculature and the heart, as well as cross-talk with endothelin ET₄ receptors at the level of caveolae/lipid rafts. These effects occur through different mechanisms that may involve NADPH oxidase, xanthine oxidase, or mitochondrial sources of ROS, which result in the increased generation of free radicals. Increased oxidant stress may activate inflammatory mediators nuclear factor-κB and activator protein-1, which upregulate adhesion molecules and result in the vascular inflammatory phenotype. Furthermore, aldosterone may be produced locally in smooth muscle or heart. How these phenomena relate to mechanisms that lead to calcium and magnesium wasting and calcium overload after the development of hyperaldosteronism and whether they eventually contribute to oxidative stress remain unclear.

Our understanding of the physiology of magnesium has undergone considerable progress in recent years as well. We now know that cellular magnesium is tightly controlled and stable under physiological conditions and that it plays a major role in regulating cardiovascular and renal function. Despite the fact that Mg²⁺ is the second most abundant intracellular cation and the predominant divalent cation, the molecular mechanisms that regulate cellular Mg²⁺ remain elusive. Transmembrane Mg²⁺ efflux has been linked to Na⁺-dependent Mg²⁺ exchanger activity, and paracellular renal Mg²⁺ transport is regulated by paracellin-1. Although studies of Mg²⁺ fluxes in mammalian cells have indicated the presence of functionally active plasma membrane Mg²⁺ transport mechanisms, the proteins responsible for these fluxes were unknown. This changed with the recent breakthrough that ion channel transient receptor potential melastatin (TRPM) 6 and TRPM7 are Mg²⁺-permeable ion channels involved in Mg²⁺ influx in epithelial and neuronal cells. TRPM6 and -7 are unique in that they are polyepptides with dual-function ion channel/protein kinases and have accordingly been termed chanzymes. TRPM6 is preferentially expressed in the small intestine, colon, and kidney, whereas TRPM7 is more widespread. TRPM7 is regulated by intracellular levels of Mg.ATP (adenosine triphosphate) and is strongly activated when Mg.ATP falls below 1 mmol/L. It was recently demonstrated that TRPM6 and -7 are expressed in vascular cells. Furthermore, TRPM7 is critically involved in vascular smooth muscle cell Mg²⁺ influx, and vascular TRPM6 and -7 are upregulated by aldosterone and angiotensin II. These findings are particularly interesting within the context of the study by Chhokar et al because they may provide insights into mechanisms underlying the hypomagnesemia and intracellular Mg²⁺ overload reported in aldosterone/salt-treated rats. It now is important to know whether in fact TRPM6 and -7 function is altered in hyperaldosteronism, and such studies certainly warrant further consideration.

Chhokar et al demonstrate that lymphocyte generation of ROS (H₂O₂) is temporally linked to Ca²⁺ overload, suggesting a causal association between oxidant stress and a proinflammatory phenotype in hyperaldosteronism. Although it is tempting to attribute oxidative stress to intracellular Ca²⁺ excess, especially because mitochondrial matrix Ca²⁺ overload has been shown to enhance the generation of ROS, the present study did not establish a causal relationship between changes in calcium and oxidant excess. Mechanisms leading to the increased generation of ROS have been investigated in previous studies, and from these it appears that aldosterone itself, in the presence of inappropriate sodium intake or balance, will result in activation of NADPH oxidase, xanthine oxidase, or mitochondrial sources of ROS. Furthermore, changes in Mg²⁺ status may directly influence the cellular...
redox state. Mg$^{2+}$ deficiency is associated with the increased production of ROS and the induction of immune and inflammatory reactions.22–24 The intermediate steps from mineralocorticoid receptors to the source of increased oxidant stress remain unclear. For other agents stimulating ROS generation such as angiotensin II, these pathways have been delineated and involve c-src,25 protein kinase C,26 and phospholipase D.27 Whether these molecular steps mediate some of the actions of aldosterone must be clarified by further studies. For the time being, the pathophysiological relationships involved in the association between hyperaldosteronism, calcium and magnesium wasting, tissue calcium overload (in particular, in the heart, leading to cardiac failure), and oxidative stress remain undefined. The study by Chhokar et al2 proposes an attractive hypothesis that requires further investigation.

References
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