Mineralocorticoid and SGK1-Sensitive Inflammation and Tissue Fibrosis

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Key Words

Mineralocorticoid receptor · T_H17 cells · TGF-β · SGK1 · Connective tissue growth factor

Abstract

Effects of mineralocorticoids are not restricted to regulation of epithelial salt transport, extracellular volume and blood pressure; mineralocorticoids also influence a wide variety of seemingly unrelated functions such as inflammation and fibrosis. The present brief review addresses the role of mineralocorticoids in the orchestration of these latter processes. Mineralocorticoids foster inflammation as well as vascular, cardiac, renal and peritoneal fibrosis. Mechanisms involved in mineralocorticoid-sensitive inflammation and fibrosis include the serum- and glucocorticoid-inducible kinase 1 (SGK1), which is genomically upregulated by mineralocorticoids and transforming growth factor β (TGF-β), and stimulated by mineralocorticoid-sensitive phosphatidylinositol 3-kinase. SGK1 upregulates the inflammatory transcription factor nuclear factor-κB, which in turn stimulates the expression of diverse inflammatory mediators including connective tissue growth factor. Moreover, SGK1 inhibits the degradation of the TGF-β-dependent transcription factors Smad2/3. Mineralocorticoids foster the development of

T_H17 cells, which is compromised following SGK1 deletion. Excessive SGK1 expression is observed in a wide variety of fibrosing diseases including lung fibrosis, diabetic nephropathy, glomerulonephritis, obstructive kidney disease, experimental nephrotic syndrome, obstructive nephropathy, liver cirrhosis, fibrosing pancreatitis, peritoneal fibrosis, Crohn's disease and celiac disease. The untoward inflammatory and fibrosing effects of mineralocorticoids could be blunted or even reversed by mineralocorticoid receptor blockers, which may thus be considered in the treatment of inflammatory and/or fibrosing disease.

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Introduction

Mineralocorticoids are decisive hormones in the regulation of extracellular volume homeostasis [1–3]. They are released following extracellular volume depletion and restore extracellular volume by stimulating salt intake [4, 5] and curtailing renal salt loss [2]. Extracellular volume expansion increases cardiac output and thus blood pressure [1, 6]. However, mineralocorticoids participate in the regulation of a wide variety of further functions [7]. The present brief synopsis addresses the role of mineralo-

corticoids in the regulation of inflammation and tissue fibrosis. Specific emphasis will be placed on the role of the serum- and glucocorticoid-inducible kinase 1 (SGK1) in the mineralocorticoid action on inflammation and fibrosis. The reader is encouraged to consult earlier, more extensive reviews on mineralocorticoids and inflammation as well as tissue fibrosis [8–17].

Effect of Mineralocorticoids on Inflammation and Fibrosis

Mineralocorticoid and salt excess in rats lead to the activation of T_H17-helper cells in several tissues including the heart and kidneys [18]. The T_H17-helper cells upregulate the pro-inflammatory cytokines GM-CSF, TNF- α and interleukin (IL)-2 [19]. The effect of mineralocorticoids on T_H17 cell abundance is reversed by spironolactone treatment [18]. Application of anti-IL-17 to mineralocorticoid/salt-treated rats blunts the arterial hypertension, renal and cardiac expression of profibrotic and pro-inflammatory mediators as well as collagen deposition [18]. Mineralocorticoids further amplify activation of blood platelets [20], which in turn participate in vascular inflammation [21, 22].

The mineralocorticoid receptor is expressed in vascular smooth muscle cells and participates in vascular remodeling [23]. Mechanisms involved in mineralocorticoid regulation of vascular function include generation of reactive oxygen species by nicotinamide adenine dinucleotide phosphate oxidase and by mitochondria [24, 25], Rho-kinase signaling [23, 25, 26], activation of epidermal growth factor receptor [27], stimulation of vascular endothelial growth factor type 1 receptor [23] and galectin signaling [23]. Mineralocorticoids are effective by influencing both genomic and nongenomic mechanisms [28].

Mineralocorticoids stimulate vascular [10, 23, 24, 29–31], cardiac [8, 24, 29, 32–40], renal [24, 26, 36, 41–43], peritoneal [14, 17] and pancreatic [44] fibrosis.

Role of SGK1 in Mineralocorticoid-Sensitive Inflammation and Fibrosis

The inflammatory signaling of mineralocorticoids involves SGK1 [7, 45]. Mineralocorticoids are strong stimulators of SGK1 expression [46] and stimulate the phosphoinositide 3-kinase pathway [47, 48], which in turn activates SGK1 [46]. SGK1 expression is further upregulated by an increase in extracellular NaCl concentration

[45, 49, 50], an effect involving p38/MAPK [46]. The kinase inactivates the transcription factor Foxo1, which is in turn required for IL-23 receptor expression [50]. Via this receptor, IL-23 stimulates the generation of IL-17-producing CD4⁺-helper T cells (T_H17 cells). The T_H17 cells play a decisive role in autoimmune disease [19]. T_H17 cells are further upregulated by increased extracellular NaCl concentration [50], an effect involving p38/MAPK, SGK1 and nuclear factor of activated T cells 5 (NFAT5, TONEBP) [19]. Along those lines, high-salt diet fosters the infiltration of T_H17 cells into the central nervous system and thus aggravates the course of experimental autoimmune encephalomyelitis [19]. At least in theory, mineralocorticoid excess may thus through upregulation of SGK1 predispose to autoimmune disease.

SGK1 is decisive for mineralocorticoid- and high-salt-induced tissue fibrosis [41, 51]. Accordingly, gene-targeted mice lacking functional SGK1 are largely protected against cardiac [51] and renal [41] fibrosis following mineralocorticoid excess. Excessive SGK1 expression is observed in a wide variety of fibrosing tissues, such as lung fibrosis, diabetic nephropathy, glomerulonephritis, experimental nephrotic syndrome, obstructive nephropathy, liver cirrhosis, fibrosing pancreatitis, peritoneal fibrosis, Crohn's disease and celiac disease [41, 45, 46, 51–53]. SGK1 expression is upregulated by transforming growth factor β (TGF- β) [46], a powerful stimulator of tissue fibrosis [11, 54–59]. The fibrosing effect of TGF- β is partially mediated by upregulation of the transcription factors Smad2/3 [45]. Those transcription factors are degraded by the ubiquitin ligase Nedd4L [7, 45]. Nedd4L is phosphorylated and thus inactivated by SGK1, which thus amplifies the TGF- β effects [45]. SGK1 further activates nuclear factor- κ B (NF κ B) [46], a transcription factor fostering inflammation and fibrosis [45, 60, 61]. SGK1 phosphorylates and thus activates the kinase IKK, which in turn phosphorylates the NF κ B inhibitory protein I κ B [46, 51]. The phosphorylation triggers the degradation of I κ B, thus leading to disinhibition and nuclear translocation of NF κ B [46, 51]. NF κ B-sensitive genes include connective tissue growth factor (CTGF), which is involved in fibrosis [46, 51]. SGK1-dependent expression of CTGF contributes to the mineralocorticoid stimulation of cardiac fibrosis [46, 51] and aging of the skin [62]. SGK1 is further involved in angiotensin II-induced cardiac CTGF formation and fibrosis [63, 64] as well as in cardiac remodeling following increased afterload [45, 65, 66].

Mineralocorticoid Receptor as a Target for Anti-Inflammatory Treatment

Mineralocorticoid-induced inflammation and tissue fibrosis is blunted or even reversed by inhibitors of the mineralocorticoid receptor, such as spironolactone or eplerenone [29, 42, 67–73]. At least in theory, untoward mineralocorticoid effects could be abrogated by inter-

ference with mineralocorticoid receptor-dependent signaling, such as inhibition of SGK1 [74]. In view of the existing knowledge, it is tempting to speculate that mineralocorticoid receptor blockade or inhibition of mineralocorticoid receptor-dependent signaling favorably influences the clinical course of autoimmune and fibrosing disease.

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