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Review

Cross-talk between aldosterone and angiotensin signaling in vascular smooth muscle cells

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ABSTRACT

In hypertension or other forms of cardiovascular disease, the chronic activation of the renin-angiotensin-aldosterone system (RAAS) leads to dysfunction of the vasculature, including, increased vascular tone, inflammation, fibrosis and thrombosis. Cross-talk between the main mediators of the RAAS, aldosterone and angiotensin (Ang) II, participates in the development of this vascular dysfunction. Recent studies have highlighted the molecular mechanisms supporting this cross-talk in vascular smooth muscle cells (VSMCs). Some of the signaling pathways activated by the Ang II type 1 receptor (AT_1R) are dependent on the mineralocorticoid receptor (MR) and vice versa. VSMC signaling pathways involved in migration and growth are under the control of cross-talk between aldosterone and Ang II. A synergistic mechanism leads to potentiation of signaling pathways activated by each agent. The genomic and non-genomic mechanisms activated by aldosterone cooperate with Ang II to regulate vascular tone and gene expression of pro-inflammatory and pro-fibrotic molecules. This cross-talk is dependent on the non-receptor tyrosine kinase c-Src, and on receptor tyrosine kinases, EGFR and PDGFR, and leads to activation of MAP kinases and growth, migration and inflammatory effects. These new findings will contribute to development of better treatments for conditions in which the RAAS is excessively activated.

Contents

Under physiological conditions, the renin-angiotensin-aldosterone system (RAAS) is activated in response to decreases of blood pressure or salt and extracellular fluid volume. The liver-produced angiotensinogen is cleaved by renin secreted by the juxtaglomerular cells of the renal afferent arteriole in the kidney to generate angiotensin (Ang) I. Ang II is the product of the cleavage of Ang I by angiotensin converting enzyme mainly during passage through the lungs but also in peripheral tissues. Ang II

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stimulates the secretion of aldosterone by the zona glomerulosa of the adrenal cortex. Ang II and aldosterone are the main effectors of RAAS system that will induce an increase in blood pressure and retain salt and water. Ang II and aldosterone have vasoconstrictor action and are anti-natriuretic leading to an increase in vascular resistance and blood volume. In addition to their physiological effects on blood pressure and salt and fluid volume homeostasis, Ang II and aldosterone are involved pathophysiologically in the development of cardiovascular conditions such as hypertension, atherosclerosis, and heart failure. Recent work has demonstrated that Ang II and aldosterone have synergistic effects on target organs that could be involved in the development of hypertension. This review focuses on the studies that have examined the cross-talk between Ang II- and aldosterone-induced cell signaling in the vasculature, particularly at the level of the smooth muscle layer.

1. Angiotensin type 1 receptor

The G protein-coupled receptors (GPCRs) Ang II type 1 (AT_1R) and type 2 (AT_2R) receptors mediate the effects of Ang II. AT_1R signaling pathways have been reviewed elsewhere [22,40]. AT_1R will only be the subject of a brief overview here. In rodents, AT_1R has two isoforms (AT_{1a} and AT_{1b}), encoded by two genes. The human genome in contrast contains only one gene. AT_1R is a potent activator of many signaling pathways in vascular smooth muscle cells (VSMCs) participating in its constrictor, migratory, growth promoting, proliferative and apoptotic effects. In the vasculature, pathophysiological consequences of excessive AT_1R activation are arterial remodeling, inflammation, fibrosis, and atherosclerosis. AT_1R presents a basal activity that is independent of ligand occupancy of the receptor, and that increases with its level of expression [47]. As a GPCR, it may bind directly to trimeric G proteins, GPCR kinases and β-arrestins [37]. GPCR kinases phosphorylate AT_1R and desensitize it. The phosphorylated receptor binds to β-arrestins and is internalized in chlathrin coated pits. Part of the internalized receptors is routed to lysosomes where they are degraded, and the remainder is recycled to the membrane [5]. AT_1R-associated protein (ATRAP) directly binds AT_1R to inhibit its signaling [4,16]. AT_1R is activated by mechanical stretch independently of Ang II binding [47]. This mechanical activation is blocked by the inverse agonists losartan [36] and candesartan [47].

Immediate signaling in response to Ang II and leading to contraction involves the production of inositol triphosphate (IP3), which acts on intracellular stores to release calcium and increase intracellular calcium concentrations. The Rho/Rho kinase pathway that sensitizes contractile proteins to calcium is activated by Ang II action [38]. AT_1R activates phospholipase A2 to produce arachidonic acid. Cyclooxygenases, lipoxygenases and cytochrome P450 enzymes metabolize arachidonic acid to produce eicosanoids that regulate the contractility of VSMCs [40]. AT_1R-induced activation of phospholipase D leads to the hydrolysis of phosphatidylcholine to produce phosphatidic acid, which can be transformed into diacylglycerol, an activator of conventional and novel classes of protein kinase type C (PKC). A major signaling pathway of AT_1R that is involved in its adverse effects contributing to inflammation is the activation of NADPH oxidase which generates superoxide anions [41]. Together with the production of oxidative stress, the activation of transcription factor NF-κB is crucial for Ang II to exert its pro-inflammatory properties. NF-κB is responsible for the induction of expression of the pro-inflammatory molecules VCAM-1, MCP-1 and IL-6 by Ang II [20]. Migratory and pro-proliferative effects of AT_1R are dependent on the activation of extracellular signal-activated kinases (ERK)1/2, p38 mitogen activated protein (MAP) kinase (p38) and c-Jun kinase (JNK) pathways. Activation of ERK1/2 and p38 is dependent on transactivation of epidermal growth factor receptor (EGFR) by a mechanism involving a metalloprotease [31]. Further to its role in downregulation of AT_1R, β-arrestins have been involved in its signaling. In VSMCs, AT_1R activates two distinct signaling pathways dependent on β-arrestins or G-proteins that together contribute to EGFR transactivation [12].

2. Angiotensin type 2 receptor

In the vasculature, AT_2R has opposite effects to those of AT_1R [11]. It is expressed in the vasculature in endothelial cells and in VSMCs of striated muscle [28]. No G protein coupling has been found for AT_2R. Its binding with AT_2R interacting protein-1 (ATIP-1) may be involved in its homodimerisation [32]. In the vasculature, AT_2R has vasodilatory effects dependent on the activation of the nitric oxide (NO)/cGMP pathway [33]. It has been hypothesized that the vasodilator properties of AT_2R are involved in the beneficial cardiovascular effect of AT_1R or angiotensin receptor blockers (ARBs). In the presence of ARBs, the circulating levels of Ang II increase, which may activate AT_2R, which could supply additional beneficial effects to the AT_1R blockade.

3. Mineralocorticoid receptor

Aldosterone effects are mediated by activation of the MR. Two clinical studies (RALES [30] and EPHESUS [29]), demonstrated that antagonizing MR in addition to standard therapy decrease the mortality in patients with severe heart failure (RALES) or left ventricular dysfunction after myocardial infarction (EPHESUS). These studies have emphasized the need for a better knowledge of aldosterone-mediated effects in the cardiovascular system. Aldosterone effects are mediated by genomic (long term) and non-genomic (rapid) pathways.

4. Genomic effects of aldosterone

MR is a ligand-activated transcription factor that is a member of the nuclear receptor superfamily. It has three functional domains, an N-terminal domain (NTD), a DNA-binding domain (DBD), and a hinge region linking them to a C-terminal ligand-binding domain (LBD) [42]. In absence of 11β-hydroxysteroid dehydrogenase 2 (HSD11B2), MR binds cortisol that is present in many-fold higher concentration in serum and tissues than aldosterone. The inactivation of cortisol to cortisone by HSD11B2 is necessary for aldosterone to exert effects by activation of MR [7,10]. In the cytoplasm, MR is bound to chaperone proteins. Upon ligand activation, MR dissociates from the chaperone proteins, dimerises and translocates to the nucleus where it binds to the hormone response element (HRE). In the kidney, MR regulates gene expression of proteins that handle electrolyte homeostasis such as Na^+/K^+ ATPase, the epithelial sodium channel (ENaC) and the renal outer medullary potassium channel [46]. The identity of co-regulators that bind to MR defines its inhibitory or activator effect on transcriptional activity. In VSMCs, aldosterone activates expression of genes involved in fibrosis, calcification and inflammation [10]. It regulates the expression of the parathyroid hormone receptor (PTHR), bone morphogenic protein 2 (BMP2), bone-liver-kidney alkaline phosphatase (AlkPhos), interleukin-16 (IL-16), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4). Aldosterone-induced proliferation of VSMCs is dependent on increase in the expression of p53 binding protein, MDM2 [27].

5. Non-genomic effects of aldosterone

In addition to its genomic effects, aldosterone has immediate early signaling effects independent of its translocation to