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Review

New aspects of rapid aldosterone signaling

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ABSTRACT

Aldosterone, the endogenous ligand of the mineralocorticoid receptor (MR) in humans, is a steroid hormone that regulates salt and water homeostasis. Recently, additional pathophysiological effects in the renocardiovascular system have been identified. Besides genomic effects mediated by activated MR, rapid aldosterone actions that are independent of translation and transcription have been documented. While these nongenomic actions influence electrolyte homeostasis, pH and cell volume in classical MR target organs, they also participate in pathophysiological effects in the renocardiovascular system causing endothelial dysfunction, inflammation and remodeling. The mechanisms conveying these rapid effects consist of a multitude of signaling molecules and include a cross-talk with genomic aldosterone effects as well as with angiotensin II and epidermal growth factor receptor signaling. Rapid corticosteroid signaling via the MR has also been demonstrated in the brain. Altogether, the function of nongenomic aldosterone effects seems to be to modulate other signaling cascades, depending on the surrounding milieu.

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Aldosterone, the endogenous mineralocorticoid in humans, was first isolated in 1953 as the last of the steroid hormones (Simpson et al., 1954). In the early years, the main focus of research lay on the long-term effects of aldosterone on sodium–potassium homeostasis and regulation of blood pressure in so-called mineralocorticoid target organs like kidney, colon and salivary glands. These effects were reported to be "genomic", i.e. dependent on transcription and translation. It was discovered that aldosterone binds to the mineralocorticoid receptor (MR) in the cytoplasm, causing dissociation of chaperones and formation of MR dimers. These dimers then translocate into the nucleus and act as transcription factors to influence the expression of certain genes. Several genes were identified as being directly or indirectly regulated by aldosterone, for example Na^+–K^+ ATPase, ENaC via SGK1 and ROMK, all of them concerned with electrolyte and volume regulation (Beesley et al., 1998; Chen et al., 1999; Kolla and Litwack, 2000).

New interest in aldosterone arouse, when its effects in non-classical MC targets like VSMC, endothelial cells and cardiomyocytes were detected, showing an involvement in pathophysiological processes in the renocardiovascular system. Clinical studies demonstrated that patients with congestive heart failure or after myocardial infarction benefited from addition of MR antagonists to their treatment regiment (Pitt et al., 1999, 2003a,b). Furthermore, the frequency of an elevated renin to aldosterone ratio in patients with hypertension was shown to be much higher than previously expected, leading to a reevaluation of the importance of aldosterone in patients with hypertension (Fardella et al., 2000; Rossi et al., 2006; Connell et al., 2003). In the search for the pathomechanism responsible for these positive effects of MR antagonists, the pathophysiological function of aldosterone in the renocardiovascular system came under fierce scrutiny. It was found that aldosterone participates in inflammatory and remodeling processes in these tissues, leading to fibrosis, endothelial dysfunction and hypertrophy (Blasi et al., 2003; Brilla and Weber, 1992; Qin et al., 2003; Rocha et al., 2002; Young and Funder, 2003). Because the mechanisms of action and additional conditions required were

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not clear, researchers began to look into the different signaling pathways of aldosterone in more depth. These include the rapid nongenomic effects, which do not require transcription or translation of genes. After long debates about their actual existence and biological relevance, discussions about their receptor and signaling pathways followed. Only recently, after the new interest in the pathophysiological effects of aldosterone and after acknowledging that there is a cross-talk between genomic and nongenomic effects have the possible consequences of rapid aldosterone signaling pathways come into focus.

1. First evidence for nongenomic aldosterone signaling

After long-time neglect of rapid aldosterone effects on sodium and potassium excretion in the kidney (Ganong and Mulrow, 1958), nongenomic effects of aldosterone were first postulated by Moura and Worcel in the mid 1980s (Moura and Worcel, 1984). Early cellular studies demonstrated enhanced sodium exchange in canine erythrocytes, ruling out a genomic mechanism because of lack of a nucleus (Spach and Streeten, 1964). These studies were followed by investigations on aldosterone-mediated electrolyte transport in human mononuclear leukocytes (Wehling et al., 1989b, 1990; Christ et al., 1993). A rapid increase in sodium–proton exchange was detected which was declared nongenomic because of its rapid kinetics and insensitivity to inhibitors of translation or transcription (Wehling et al., 1989a). These early experiments explored aldosterone-dependent changes in second messenger systems without emphasis on the biological consequences. Nongenomic aldosterone-mediated signaling events described included an elevation of intracellular Ca^{2+}, IP3, DAG and PKC, PLC and cAMP (Christ et al., 1993, 1995b, 1999; Wehling et al., 1995, 1996). Importantly, these effects were shown to occur not only in renal cells but also in VSMC and endothelial cells, i.e. cells of non-classical mineralocorticoid target organs (Christ et al., 1995a; Wehling et al., 1994, 1995, 1996).

Much controversy arouse about the receptor conveying these effects. Early studies suggest that the nongenomic effects are mediated by a membrane receptor distinct from the classical cytoplasmic MR. Arguments supporting this concept include the rise in Ca^{2+} and cAMP found in cultured skin cells from MR knockout mice (Haseroth et al., 1999). Furthermore, antagonists against the classical MR like canrenone and spironolactone were not always able to inhibit the rapid effects of aldosterone (Good et al., 2002). In several studies, glucocortoicoids, which bind to the classical MR with an affinity comparable to that of aldosterone, could not elicit the same rapid effects as aldosterone (Doolan and Harvey, 1996a). And last, aldosterone coupled to large molecules like BSA and therefore unable to cross the membrane rapidly, elicited the same rapid effects, favoring a membrane receptor (Le Moellic et al., 2004). Similar receptors have been proposed for other steroid hormones (Orshal and Khalil, 2004; Zhu et al., 2003). However, there are several arguments against a structurally different MR responsible for nongenomic effects as well. Firstly, more flexible and water-soluble MR antagonists like RU28318 are able to inhibit the same nongenomic aldosterone effects that cannot be inhibited by spironolactone (Michea et al., 2005; Mihailidou and Funder, 2005). Secondly, Alzamora and colleagues show in an elegant study that the lack of response to cortisol is due to 11β-HSD. 11β-HSD is an enzyme co-localized with the MR which converts cortisol into the biologically inactive cortisone that is unable to bind to the MR. Inhibition of 11β-HSD by carbenoxolone caused cortisol to exert similar rapid effects like aldosterone (Alzamora et al., 2000). And thirdly, in a heterologous expression system of HEK cells lacking classical MR, nongenomic effects involving ERK1/2 and JNK activation could only be induced after transient transfection with the classical MR. Cells lacking this receptor showed no rapid MAP kinase activation after incubation with aldosterone (Grossmann et al., 2005). Nevertheless, the same heterologous cell system revealed a rise in intracellular Ca^{2+} that is independent of the classical MR (Grossmann et al., 2005). Overall, the existence of nongenomically mediated aldosterone effects that seem to be mostly dependent on the classical MR and activate a variety of second messengers in both classical and non-classical MR target organs was established in the early phase of rapid aldosterone research (Table 1). These studies were followed by more in depth investigations on the signaling cascades involved and the pathophysiological effects conveyed.

2. Nongenomic aldosterone effects in classical mineralocorticoid target organs

In classical mineralocorticoid target organs like kidney and colon, a rapid effect of aldosterone on intracellular pH is detectable; a transient acidification is followed by a significant alkalization in both MDCK and M1 cells (Gekle et al., 1996; Markos et al., 2005; Wehling et al., 1996). There is much evidence that the rise in pH is caused by a rapid increase in intracellular Ca^{2+} followed by activation of the sodium–proton exchanger (NHE) (Doolan and Harvey, 1996b; Oberleithner et al., 1987; Gekle et al., 2001; Markos et al., 2005). In MDCK cells, prerequisite for this process is a net entry of Ca^{2+} from outside the cell and a plasma membrane proton conductance to stimulate the NHE (Gekle et al., 1996). As source for the enhanced NHE activity, an increase in proton affinity was identified. When inhibiting NHE activity by a sodium free environment, proton conductance activation was unmasked and aldosterone induced a membrane potential-dependent acidification in MDCK and M1 cells. As shown by pharmacological studies, this process relies on PKC and heterotrimeric G proteins (Gekle et al., 1997). Furthermore, Harvey et al. demonstrated that aldosterone-induced activation of PKCα leads to a rapid increase in intracellular calcium through verapamil-sensitive ion channels, which then activates the NHE (Doolan et al., 1998; Harvey et al., 2002). The increase in pH then causes activation of a pH sensitive potassium channel K_{ATP} and inhibition of Ca^{2+}-dependent K^+-channels which lead to an increase in K^+-recycling to maintain the electrical driving force for amiloride-sensitive Na^+-absorption while Cl^--secretion is inhibited (Maguire et al., 1999). Overall, the increase in intracellular sodium causes a change in cell volume that can be monitored by atomic force microscopy (Schneider et al., 1997b). These effects are insensitive to actinomycin D or cycloheximide. Further signaling molecules involved are the MAP kinases ERK1/2. Inhibitors of ERK1/2 phosphorylation are able to inhibit both the increase in intracellular Ca^{2+} and the activation of NHE. Preventing the increase in intracellular Ca^{2+} eliminates NHE stimulation but not ERK phosphorylation (Gekle et al., 2001). These results suggest that activation of NHE is mediated by an ERK-dependent increase in intracellular Ca^{2+} in MDCK cells. Upstream of ERK1/2, aldosterone induces phosphorylation of the epidermal growth factor receptor (EGFR). Alternatively, PKC-induced activation of ERK1/2 followed by stimulation of NHE has also been demonstrated in other cell types (Markos et al., 2005). Several investigators identified c-src as the link between aldosterone-bound MR and MAP kinases often with EGFR as intermediate (Callera et al., 2005b; Grossmann et al., 2005; McEneaney et al., 2007). Activation of ERK1/2 was dependent on the classical MR but analogous to the progesterone and the estrogen receptor, deletion constructs containing only the MR domains E/F were sufficient (Grossmann et al., 2008). Additionally, involvement of heat shock protein 90, the chaperone of the classical MR, has been reported (Braun et al., 2004; McEneaney et al., 2007). Besides regulating the ubiquitous basolateral NHE1, aldosterone also decreases apical NHE3 activity in the medullary thick