Mineralocorticoids: The Secret of Muscle Reflex Dysfunction in Hypertension?

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Hypertension is one of the most common human disorders, affecting ~26% of the adult population worldwide(9). Half of all strokes and ischemic heart disease events are attributable to high blood pressure (BP). It has been well reported that the cardiovascular response to exercise is exaggerated in hypertensive patients and characterized by augmented increases in arterial BP, heart rate (HR), and sympathetic nerve activity (SNA)(1; 17; 19; 27). Considering that these patients already have high BP, the exaggerated exercise-evoked sympathetic and pressor responses could further increase the risk for adverse cardiovascular or cerebrovascular events including myocardial ischemia, myocardial infarction, cardiac arrest and/or stroke during or immediately following a bout of exercise. Therefore, it is extremely important to understand the potential mechanisms underlying the exaggerated cardiovascular response to exercise in hypertension. In the past decade, a series of studies from Smith and colleagues have made significant contributions to this field. In general, evidence from their laboratory suggest that an overactive exercise pressor reflex (EPR), a peripheral neural reflex originating in skeletal muscle, contributes to this abnormal cardiovascular responsiveness during exercise in several hypertensive rodent models (11; 14; 15; 24). The afferent arm of this reflex is composed of both metabolically sensitive (group IV, C) and mechanically sensitive (group III, Aδ) fibers (7; 8).

In 2006, Smith et al. was the first to show that activation of the EPR by static muscle contraction caused greater increases in BP and HR in spontaneous hypertensive rats (SHR, a neurogenic hypertensive model) than in normotensive Wistar-Kyoto (WKY) rats (24). Furthermore, Smith and colleagues used either passive muscle stretch or hindlimb intra-arterial administration of capsaicin to preferentially activate mechanoreceptors or metaboreceptors in the triceps surae muscle. In this study(11), both mechano and metaboreflexes were augmented in SHR. Two recent studies by Mizuno and Smith (14; 15) also examined the possibility that enhanced EPR
sensitivity manifest in other hypertensive models such as prenatal programming of hypertension (PPH)- and aldosterone and salt loading-induced hypertension. It should be noted that not all hypertensive animal models exhibit an exaggerated EPR. For example, O’Leary and colleagues used a renovascular (2 kidney-1 clip, 2K1C) hypertensive canine model to document that BP, cardiac output and HR responses to metaboreflex activation during submaximal dynamic exercise are blunted in conscious 2K1C dogs compared to their responses prior to hypertension (18; 25). While this finding appears inconsistent with that described in the SHR and PPH models, this discrepancy may be due to several factors including 1) the different animal models (rats vs. canines); 2) exercise paradigms (static contraction vs. submaximal dynamic exercise); 3) surgical preparation (decerebration vs. conscious). A major difference is the preparation and the mechanisms mediating the pressor responses. It is highly likely that in the decerebrated rat preparation the rise in BP with the EPR is entirely due to peripheral vasoconstriction which is exaggerated in SHR. In contrast, in dogs, the rise in BP is almost entirely due to increases in cardiac output. In the study by Spranger et al. (25), the authors concluded that there was a shift towards more vasoconstriction in hypertension inasmuch as the normal vasodilation (likely due to epinephrine release) was attenuated. So, both preparations would support enhanced peripheral vasoconstriction in response to exercise in hypertension. Further studies should be carried out to address this discrepancy.

In the current paper(3), Downey et al. further attempted to address the potential mechanism underlying the exaggerated EPR in SHR rats. They examined the effects of mineralocorticoid receptor (MR) antagonists (spironolactone, SPIR; eplerenone, EPL) on the EPR in both WKY and SHR rats. The authors used static contraction to activate the EPR whereas muscle passive stretch was used to selectively activate the mechanoreflex. The primary finding of this study is
that both chronic SPIR and EPL administration attenuated the exaggerated EPR as well as the mechanoreflex in SHR rats whereas they had no effect in the normotensive WKY rats. Generally, this study suggests that MR/aldosterone signaling plays a critical role in mediating the exaggerated EPR in the hypertensive rather than normotensive states. A potential limitation of this study is that the authors did not verify the effective target of mineralocorticoid antagonists (central vs. peripheral). It is possible that single/multiple components of the EPR reflex arc including sensory afferents, the spinal cord or cardiovascular regions in the brain stem could be affected by this systemic administration. Figure 1 summarized the potential sites where the EPR reflex arc may be targeted by MR/aldosterone signaling in hypertension. The remainder of this Editorial Focus will offer several discussion points further identifying potential targets of aldosterone/MR signaling in the reflex arc of the EPR.

MR and the endogenous ligand, aldosterone, are best known for their control of the water and electrolyte balance at the renal level and their involvement in volume and BP regulation (26). Recently, there is a growing interest in the role of the peripheral MR/aldosterone axis to modulate sensory afferent activity (2; 13; 21). For example, a recent study by Shaqura et al.(21) demonstrated that in naive Wistar rats using double immunofluorescence confocal microscopy of the spinal cord, dorsal root ganglia, sciatic nerve and innervated skin revealed that MR predominantly colocalized with calcitonin-gene-related peptide (CGRP)- and trkA-immunoreactive (IR) nociceptive neurons and only marginally with myelinated trkB-IR mechanoreceptive and trkC-IR proprioceptive neurons underscoring a pivotal role for MR in the modulation of nociceptor function. It will be worthwhile for the authors to compare the aldosterone levels as well as protein expression of MR in local dorsal root ganglia (DRG) between WKY and SHR rats in future experiments. Direct recordings of muscle mechanical and
metabolic afferent activity will be helpful to address whether systemic administration of MR antagonists alter the muscle afferent sensitivity in SHR rats. Based on the study by Shaqura et al. (21), it is also likely that the spinal cord may be influenced by systemic administration of MR antagonists since the dorsal horn of the spinal cord exhibits a high level of MR expression. The dorsal horn of the spinal cord serves as the first central synapse for afferent fibers from skeletal muscle. Neurotransmitters and neuromodulators released by contraction-activated group III and IV muscle afferents into this region initiate the central component of the EPR. Evidence suggests that the EPR transmission at the level of the dorsal horn is mediated by both excitatory and inhibitory neurotransmitters (glutamate and GABA) (5; 6; 28; 29). On the other hand, aldosterone had been reported to interact with both glutamatergic and GABAergic pathways in the dorsal horn (4; 16). Therefore, it is possible that spinal MR/aldosterone signaling may be involved in the genesis of the exaggerated EPR in SHR rats. Last, but not least, previous studies from Smith and colleagues (10; 23) suggest that the cardiovascular centers in brain stem, such as the nucleus tractus solitarius (NTS) play a critical role in modulation of the EPR. Parallel evidence also suggests that MR/aldosterone signaling modulates the NTS neuronal activity (12; 20; 22). Therefore, the NTS may be another potential site that mediates the MR/aldosterone-mediated exaggerated EPR in hypertension.

In conclusion, the current paper by Downey and colleagues (3) discovered a novel role of MR/aldosterone signaling in modulating the exaggerated EPR in hypertension. Effective treatment of EPR overactivity via inhibition of MR/aldosterone signaling may reduce the cardiovascular risks associated with physical activity in hypertension. Future studies are needed to further verify the potential targets affected by MR/aldosterone signaling in hypertension.

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Disclosures

None.


**Figure Legend.**

**Figure 1.** A schematic diagram summarizing the potential sites of the EPR reflex arc targeted by mineralocorticoid receptor (MR)/aldosterone signaling in hypertension. NTS, nucleus tractus solitaries. RVLM, rostral ventrolateral medulla. Blue line represents ascending signals and red line represents descending signals.