A review of deoxycorticosterone acetate-salt hypertension and its relevance for cardiovascular physiotherapy research

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Abstract. [Purpose] The purpose of this review was to elucidate the deoxycorticosterone acetate (DOCA)-salt-related hypertensive mechanism and to contribute to future studies of cardiovascular physiotherapy. [Methods] This paper focuses on the signal transductions that control hypertension and its mechanisms. We include results reported by our laboratory in a literature review. [Results] Our results and the literature show the various mechanisms of DOCA-salt hypertension. [Conclusion] In this review paper, we carefully discuss the signal transduction in hypertension based on our studies and with reference to cardiovascular physiotherapy research.

Key words: Deoxycorticosterone acetate-salt hypertension, Signal transduction, Cardiovascular physiotherapy

INTRODUCTION

An increase in sympathetic activity has been generally reported to have an intimate relation with the trigger and exacerbation of hypertension. Understanding hypertension and its mechanisms is very important in specialized cardiovascular physiotherapy. The development of hypertension is also associated with altered vascular reactivity and increased transmural pressure or stretch, which directly affects vascular smooth muscle cells. The vascular smooth muscle is an important effector in the regulation of vasomotor tone. In particular, a structural and functional impairment in the regulation of vascular smooth muscle contraction may be important in the pathogenesis and maintenance of increased peripheral vascular resistance in hypertension. The total peripheral resistance and the vascular reactivity to contractile agonists are increased in patients and experimental animal models with essential and secondary hypertension. Various experimental animal models have been used in the research of the pathophysiology of hypertension. Spontaneously hypertensive rats have been widely used as a pathophysiological animal model of genetically linked hypertension such as a human essential hypertension. The Dahl salt-sensitive rat was developed by selective breeding of rats for sensitivity or resistance to the hypertensive effects of a high salt diet, and the first experimental model of renovascular hypertension via a two-kidney, one clip maneuver demonstrated that renal ischemia is the cause of this disease. Specifically, the deoxycorticosterone acetate (DOCA)-salt hypertensive models, models of volume-expanded hypertension, were used to describe the natural history of malignant hypertension and the biochemical and hormonal characteristics of each stage of the
The purpose of this review was to collate the body of knowledge on DOCA-salt hypertension and the signal transduction involved in order to prepare a basic reference for cardiovascular physiotherapy research.

**REVIEW**

**Deoxycorticosterone acetate-salt hypertension and physiotherapy**

One cause of hypertension is generally excessive salt consumption in conjunction with stress, which has a direct correlation with the DOCA-salt hypertensive model. In reality, when an increase in blood pressure occurs, the blood flow and volume are elevated by retention of water and sodium in the renal tubule, which is affected by the renin-angiotensin-aldosterone axis exposure to chronic stress. In our experimental process, which was in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996), the animals underwent uninephrectomy via flank incision under intramuscular anesthesia. After DOCA implantation surgery, DOCA-salt hypertensive rats received 0.9% NaCl plus 0.2% KCl drinking solution. Induction of DOCA-salt hypertension is directly related to the increased vascular resistance that is widely known to be caused by an increase in vessel wall tension or other factors related to tension. Several previous studies have indicated that electrical stimulation, massage, moxibustion, medicinal herbs such as Ligusticum wallichii and cordycepin and electroacupuncture may be used as alternative therapies for hypertension in particular, but more systematic and scientific physiotherapy studies are still needed.

**Abnormal vascular tension caused by stimuli and deoxycorticosterone acetate-salt hypertension**

It has been widely reported that hypertension is characterized by an increased responsiveness to vasoconstrictor agonists. In previous studies, catecholamine supersensitivity has preceded the development of hypertension. Specifically, the DOCA-salt hypertensive model is associ...
ated with marked changes that regulate vascular smooth muscle contraction due to increased adrenoceptor reactivity and activation of the sympathetic nervous system\textsuperscript{21}). Actually, the responsiveness of vasculature to norepinephrine is increased in DOCA-salt hypertension\textsuperscript{22, 23}). 5-Hydroxytryptamine markedly increases when contractions are stimulated in vascular smooth muscle strips isolated from animal models of experimental and/or genetic hypertension compared with normotensive animals\textsuperscript{24, 25}). Furthermore, one of our previous studies was the first to demonstrate that vasoconstrictors such as endothelin-1 (ET-1) decreased muscle contractility and the activity of p38 MAPK in aortic smooth muscle from DOCA-salt hypertensive rats compared with normotensive rats\textsuperscript{5}). These results imply that the MAPK pathway plays a central role in the control of muscle contraction and DOCA-salt hypertension\textsuperscript{5, 22)}.

Epidermal growth factor (EGF), one of the various growth factors, is an important regulator of cell regulation in a variety of cells\textsuperscript{7, 26}). EGF, a mitogenic polypeptide with a molecular weight of approximately 6 kD, is excreted in human urine in nanomolar quantities\textsuperscript{26}). It is also found in platelets, kidneys, and salivary glands\textsuperscript{27–29}). EGF, once released, can bind to its receptors found on vascular smooth muscle cells, in the submandibular gland, and in the rat liver\textsuperscript{30}). Although EGF acting via its tyrosine kinase receptor is widely recognized for its mitogenic and acid-inhibitory activity\textsuperscript{31}), it is now appreciated that this peptide can also modulate the contractility of a variety of smooth muscle cells and is related to the hypertension\textsuperscript{7, 32–34}). In kinase-inactive mutants, EGF directly activates hypertension-related MAPK family members\textsuperscript{34}). The major findings of one of our previous studies were that EGF contracts aortic smooth muscle from DOCA-salt hypertensive rats but not sham-operated rats and that EGF increases the activity of MAPK in DOCA-salt hypertensive rats\textsuperscript{7}). These findings indicate that significant changes in EGF responsiveness occur during the development of hypertension and may allow for the development of a contractile response to EGF. Moreover, the EGF receptor is activated and is capable of interacting with proteins, including Grb2, guanine nucleotide exchange factor Sos, Shc, c-Src, Ras and Raf-1, leading to activation of the tyrosine kinase-dependent MAPK pathway\textsuperscript{35}). However, in one of our previous studies, inhibition of the PI3 K pathway, but not ROCK, attenuated EGF-induced muscle contraction and MAPK activation but not SAPK/JNK in DOCA-salt hypertension. Furthermore, understanding the mechanisms of growth factor-induced contraction should be a critical issue in cardiovascular physiotherapy\textsuperscript{4}). In this review, we have summarized DOCA-salt hypertension and its mechanisms (Fig. 1). When scientific studies are performed in the fields of thermo-, hydro-, and electrotherapy, neurophysiotherapy, manipulative therapy, and therapeutic massage, we expect remarkable growth both

<table>
<thead>
<tr>
<th>Table 1. The characteristics of deoxycorticosterone acetate-salt hypertensive rats</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>Body weight (g)</td>
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<tr>
<td>4 weeks SBP (mmHg)</td>
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<tr>
<td>MCFP (mmHg)</td>
</tr>
<tr>
<td>Heart rate (b/m)</td>
</tr>
<tr>
<td>Aortic weight (mg/cm)</td>
</tr>
<tr>
<td>Wall thickness (µm)</td>
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<tr>
<td>Wall area (mm\textsuperscript{2})</td>
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<tr>
<td>Wall-to-lumen ratio</td>
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<td>Media thickness (µm)</td>
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<td>Media-lumen ratio (%)</td>
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<td>Media CSA (µm\textsuperscript{2})</td>
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<tr>
<td>Aortic CSA (mm\textsuperscript{2})</td>
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<tr>
<td>Lumen diameter (µm)</td>
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<tr>
<td>Femoral ring weight (mg)</td>
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<tr>
<td>Heart weight (g)</td>
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<tr>
<td>Heart weight (mg/100 g BW)</td>
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<tr>
<td>HW/BW (g/kg)</td>
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<tr>
<td>Heart weight (%/TBW)</td>
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<tr>
<td>LV weight (g)</td>
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<tr>
<td>RV weight (g)</td>
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<tr>
<td>VW-to-BW ratio (g/kg)</td>
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<tr>
<td>Kidney weight (g)</td>
</tr>
<tr>
<td>Kidney weight (%/TBW)</td>
</tr>
<tr>
<td>LKW/BW (g/kg)</td>
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Values are means ± SE. %/TBW indicates the % of total body weight; SBP: systolic blood pressure; MCFP: mean circulatory filling pressure; BW: body weight; HW: heart weight; VW-to-BW ratio: ventricular weight-to-body weight ratio; LKW: left kidney weight; CSA: cross-sectional area
in research and clinical applications in the field of cardiovascular physiotherapy (Fig. 1F).

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