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Research Report

# Effect of subfornical organ lesion on the development of mineralocorticoid-salt hypertension

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ABSTRACT

Accumulating evidence suggests that structures within the lamina terminalis; the organum vasculosm of the lamina terminalis (OVLT), the median preoptic nucleus (MnPO) and/or the subfornical organ (SFO); are required for the development of DOCA-salt hypertension. Lesion of the anteroventral tissue lining the third ventricle (AV3V), which destroys cell bodies in the OVLT and MnPO, as well as efferent projections from the SFO to the OVLT and MnPO, abolishes DOCA-salt hypertension in the rat. However, the individual contribution of these structures to DOCA-salt hypertension is unknown. The present study was designed to determine whether an intact SFO is required for hypertension development in the DOCA-salt model. In uninephrectomized SFO lesioned (SFOx; $n=6$) and SHAM ($n=8$) Sprague-Dawley rats, 24-h mean arterial pressure (MAP) and heart rate (HR) were continuously recorded telemetrically 4 days before and 36 days after DOCA implantation (100 mg/rat; s.c.); 24-h sodium and water balances were measured throughout the protocol. No differences in control MAP, HR, sodium and water balances were observed between groups. Following DOCA implantation, the magnitude of the elevation of MAP was similar between groups (~40 mm Hg) so that by Day 40, MAP was 148±5 mm Hg in SFOx and 145±4 mm Hg in SHAM rats. The magnitude of decrease in HR from control values was similar in both groups. Differences in sodium and water balances were not observed between groups. We conclude that the SFO alone does not play a significant role in the development of mineralocorticoid-salt hypertension.



## 1. Introduction

Long-term salt sensitivity of arterial pressure is a significant clinical problem in both the normotensive and hypertensive human populations. It is currently estimated that 25% of the normotensive population is "salt-sensitive" in that their arterial pressures are abnormally responsive to changes in dietary sodium chloride intake (Weinberger, 1996; Weinberger et al., 2001). This is clinically significant since the salt sensitivity of arterial pressure may be a more accurate predictor of future cardiovascular disease and morbidity than the basal level of arterial pressure itself (Weinberger et al., 2001). This condition is more prevalent in humans with essential hypertension, with estimates ranging from 50 to 75%

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of these patients exhibiting increased salt sensitivity of arterial pressure (Weinberger, 1996). Despite the clinical importance of salt-dependent hypertension, its pathogenesis is poorly understood.

Much of the previous research on salt-dependent hypertension has focused on endocrine control of sodium transport in renal tubules. Indeed, the role of the renin–angiotensin–aldosterone axis in the regulation of sodium and water balance and hypertension has been extensively studied. More specific to the present study, chronic increases in mineralocorticoids such as aldosterone or its precursor, deoxycorticosterone (DOC), result in salt dependent hypertension in experimental animals (Crofton et al., 1979; Miller et al., 1979; Takeda and Bunag, 1980; Berecek et al., 1982; Fink et al., 1987; Jacob et al., 2005). Both DOC and aldosterone bind to mineralocorticoid receptors (MRs) in the distal collecting duct of renal tubules, leading to increased synthesis of the epithelial sodium channels (ENaCs), which enhances transpepithelial sodium flux from the tubular lumen to blood (Fuller and Young, 2005). Experimental hypertension produced in animals by exogenous administration of aldosterone, DOC or its water soluble form deoxycorticosterone acetate (DOCA) has been characterized in several species including mice (Obst et al., 2004), rats (Crofton et al., 1979; Berecek et al., 1980; Takeda and Bunag, 1980; Matsuguchi and Schmid, 1982; Mento et al., 1984; Fink et al., 1987; Nishimura et al., 1998; Keep et al., 1999; Wang et al., 2003; Jacob et al., 2005), dogs (Conway and Hatton, 1966; Bravo et al., 1977) and pigs (Berecek and Bohr, 1978; Miller et al., 1979; O'Hagan and Zambraski, 1986).

In contrast to the renal-based theory of mineralocorticoid hypertension, several lines of evidence suggest that activation of the sympathetic nervous system may be responsible for the long-term increase in arterial pressure in this model. First, indirect and direct measures of sympathetic nerve activity suggest it is elevated in DOCA-salt animals (Clarke et al., 1970; Berecek et al., 1980; Takeda and Bunag, 1980; Matsuguchi and Schmid, 1982; Mento et al., 1984; De Champlain et al., 1989; Nishimura et al., 1998). Second, chronic infusion of aldosterone into the cerebral ventricles of rats (Gomez-Sanchez, 1986; Gomez-Sanchez, 1991; Wang et al., 2003) and dogs (Kageyama and Bravo, 1988) produces hypertension. Third, DOCA-salt hypertension can be completely blocked by intracerebroventricular administration of MR antagonists (Gomez-Sanchez et al., 1990; Janiak et al., 1990) and drugs that block ENaCs such as amiloride and its analogue benzamil (Nishimura et al., 1998; Keep et al., 1999). Forth, bilateral renal denervation markedly attenuates DOCA-salt hypertension (Jacob et al., 2005). Fifth, a recent study suggests that MRs and ENaCs are present throughout the lamina terminalis (Amin et al., 2005), an area that is critical to the maintenance of body fluid homeostasis (Johnson and Loewy, 1990; McKinley et al., 2003) and modulation of sympathetic nerve activity (Brody et al., 1978). Finally, lesion of the anteroventral third ventral (AV3V) region, which incorporates much of the lamina terminalis, has been shown to abolish DOCA-salt hypertension (Berecek et al., 1982). Taken together, these studies are consistent with the hypothesis that mineralocorticoids produce salt-dependent hypertension by stimulation of MRs within the lamina terminalis and subsequent activation of the sympathetic nervous system.

The lamina terminalis is composed of three structures; two of these, the subfornical organ (SFO) and organum vasculosm of the lamina terminalis (OVLT) are circumventricular organs, and the third is the median preoptic nucleus (MnPO) which sits behind the blood–brain barrier (McKinley et al., 2003). Since circumventricular organs are characterized by a poor blood–brain barrier both the SFO and OVLT are potentially responsive to circulating hormones known to cause hypertension. However, the contribution of individual structures of the lamina terminalis to these models of hypertension is not clear. For example, lesion of the AV3V abolishes angiotensin II-induced hypertension which is consistent with the localization of AT1 receptors in the SFO, MnPO and OVLT (Phillips et al., 1993). We have recently shown that lesion of the SFO alone attenuates angiotensin-induced hypertension (Hendel and Collister, 2005) although this has not been consistently found (Bruner et al., 1985). This suggests a potentially important role for the SFO in mediating hypertension caused by increased plasma concentrations of at least one component of the renin–angiotensin–aldosterone system.

The recent finding that MRs and ENaCs are present in SFO (Amin et al., 2005) led us to hypothesize that mineralocorticoid-salt hypertension is also dependent on the integrity of this circumventricular organ. We tested this hypothesis by determining the effect of electrolytic lesion of the SFO on the pathogenesis of DOCA-salt hypertension.

## 2. Results

### 2.1. *Effect of SFO lesion on cardiovascular responses to DOCA-salt hypertension*

Shown in Fig. 1 are MAP and HR responses throughout the protocol. Prior to DOCA implantation, no significant differences in basal MAP were observed between groups (SFOx=106±3 mm Hg, $n$=6; SHAM=104±4 mm Hg, $n$=8). Although MAP significantly increased from control values following DOCA implantation in both groups, the magnitude of elevation in MAP was comparable between groups (approximately 40 mm Hg). In addition, the temporal profile of the increase in MAP was similar in both groups and was characterized by an immediate pressor response followed by a slower increase in MAP. By Day 40, MAP was 148±5 mm Hg in SFOx rats and 145±4 mm Hg in SHAM rats.

During the control period, 24-h average basal heart rate was not significantly different between groups (SFOx=412±5, SHAM=404±6 beats/min). The magnitude of the bradycardic response following DOCA implantation was similar between groups such that, by Day 40, HR was 360±9 in SFOx rats and 349±8 beats/min in SHAM rats.

### 2.2. *Effect of SFO lesion on sodium and water balance responses to DOCA-salt hypertension*

During the 4-day control period, 24-h average sodium intake (SFOx=5.6±0.7, SHAM=6.3±0.8 mmol/24 h), urinary sodium