Paraventricular–suprachiasmatic lesions prevent salt-induced hypertension in Dahl rats

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Summary

1. We studied the effects that lesions produced in the paraventricular and suprachiasmatic nuclei and intervening periventricular area had on 24 h mean circadian blood pressures in Dahl salt-sensitive and -resistant rats and their sham-operated controls. We measured blood pressures while the animals were on a low salt diet and after 1, 5 and 13 weeks of 8% NaCl diet.

2. Salt-sensitive rats with lesions had lower blood pressures than salt-sensitive sham-operated controls at all points of the study. In contrast, identical lesions in salt-resistant rats produced a transient pressor response to the diet. Twenty-four hour mean heart rate, determined after 13 weeks of 8% NaCl intake, was low only in salt-sensitive rats with lesions. Sodium intake and excretion per kg of body weight, as well as plasma sodium concentrations, were similar in all groups.

3. We conclude that the anteromedial hypothalamic area, which includes the paraventricular nucleus, the suprachiasmatic nucleus and the periventricular area, participates in the development of Dahl hypertension. We suggest that a multifactorial mechanism is involved: (a) the facilitatory role of this region in ACTH release, (b) this region's participation in the baroreceptor reflex via vasopressinergic efferents to the nucleus of the tractus solitarius, and (c) the roles of the paraventricular and suprachiasmatic nuclei in the regulation of salt and water balance.

Key words: brain lesions, hypothalamus, salt hypertension, sodium metabolism.

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Abbreviations: DH, hypertension in Dahl rats (DS, salt-sensitive; DR, salt-resistant); PVE, periventricular; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus.

Introduction

The Dahl model of hypertension (DH) utilizes two strains of rats: the salt-sensitive (DS) rat develops hypertension in response to elevated dietary sodium and the salt-resistant (DR) rat does not.

Though the mechanisms of DH are unclear, evidence indicates that the kidney [1] has a primary role, but that the adrenals [2] and central nervous system [3, 4] play parts as well.

The anteromedial hypothalamic area [5], which includes the paraventricular nucleus (PVN), the suprachiasmatic nucleus (SCN) and the periventricular (PVE) area, exerts control over the hormonal, humoral and neural factors involved. We placed lesions in this brain area of Dahl rats to try to prevent the development of hypertension in DS animals receiving a high NaCl diet.

Methods

We used 40 11 week old male DS and DR rats, mean weight 359 ± 5 g, which had been fed on a 0.3% NaCl diet from the day of weaning.

After injecting 12 DS and 12 DR animals with pentobarbital to induce anaesthesia (50 mg/kg), we induced radiofrequency lesions in the PVN, SCN and PVE. Three DS and three DR rats received sham operations and three animals of each strain were subjected only to anaesthesia.

We then maintained all animals on a 0.3% NaCl diet for 3 weeks before switching them to an 8% NaCl diet for the duration of the experimental period.
Since SCN lesions alter circadian rhythms [6], we measured tail blood pressure (MK IV Physio-graph, Narco Bio-Systems, Houston, Texas, U.S.A.) every 4 h over a 24 h span at 3 weeks post-surgery, while the animals were on the 0-3% NaCl diet, and, at 1 and 5 weeks after the start of the 8% NaCl diet. After 13 weeks of maintaining the rats on the high NaCl diet, we measured heart rates as well as circadian blood pressures. We then placed all the animals in metabolic cages to equilibrate for 6 days on a high salt liquid diet (8% NaCl by dry weight) and distilled water ad libitum, before collecting 24 h urine samples and determining food and water intakes.

As the final step of our experiment, we anaesthetized the animals with intraperitoneal injection of Inactin (the sodium salt of ethylmalonylthiourea at 100 mg/kg body weight), collected a blood sample to determine plasma sodium concentration, and then the brains were removed and processed for morphological studies as described previously [6].

Using Student’s unpaired t-test, we compared urine and plasma sodium values as well as other variables of each lesion group vs control group.

**Results**

Lesions which were effective in preventing hypertension in DS rats included complete, or near-complete, destruction of the PVN, PVE and SCN; ineffective lesions spared portions of these nuclei, and were more anteriorly placed. Maximal lesion extent was approximately 1 mm from the midline with an average extent closer to 0.5 mm. In this report we will refer only to the effective lesions.

DS rats with effective lesions had lower 24 h mean blood pressures and heart rates than those of control rats (Table 1). The lesions produced no effects in either strain in any of the metabolic study variables we assessed or in plasma sodium concentrations (Table 1).

**Discussion**

This study demonstrates that effective lesions completely prevent DH without altering sodium balance. These lesions do not affect angiotensin-induced drinking [7]. This contrasts with the effects of the anteroventral third ventricle region (AV3V) lesion, which produces hypernatraemia while only partially diminishing DH [4].

Effective lesions produced a mild, transient hypertensive response to the high salt diet in DR rats. This may reflect a strain difference in the central regulation of blood pressure.

Lesions confined primarily to the PVN were only temporarily effective in preventing hypertension in two DS animals. Three DS rats had lesions primarily in SCN and adjacent PVE. These animals had slight transient increases in blood pressure. Thus it is likely that destruction of the PVN and of the PVE lying between the PVN and SCN is necessary for complete prevention of DH. DS with effective lesions showed decreased 24 h mean heart rates. This effect could be mediated by the PVN since lesions in this area alter the baroreceptor reflex [8].

The mechanisms by which lesions in the antero medial hypothalamus prevent DH are unclear. Evidence suggests that this area could influence blood pressure by hormonal and neural mechanisms; some of these are altered in DH [2, 3]. In this area: (1) Both PVN and SCN facilitate ACTH release [5]; chronic infusions of ACTH induce hypertension [9]; SCN lesions decrease the 24 h mean ACTH by 50% [10]; and PVN

| TABLE 1. Effect of antero medial hypothalamic lesions on cardiovascular dynamics and sodium metabolism in Dahl salt-sensitive and salt-resistant rats |
|---|---|---|---|---|
| **Blood pressure (mmHg)** | DSS(6) | DSLE(5) | DRS(6) | DRLE(5) |
| 3 weeks post-lesion, 0-3% NaCl diet | 127 ± 3 | 109 ± 2* | 119 ± 2 | 121 ± 9 |
| 4 weeks post-lesion, 8% NaCl diet | 136 ± 6 | 120 ± 6 | 122 ± 6 | 121 ± 4 |
| 8 weeks post-lesion, 8% NaCl diet | 173 ± 4 | 123 ± 5* | 123 ± 3 | 133 ± 2† |
| 16 weeks post-lesion, 8% NaCl diet | 198 ± 6 | 122 ± 5* | 123 ± 5 | 125 ± 3 |
| Heart rate (beats/min), 13 weeks post-lesion | 422 ± 10 | 379 ± 13* | 408 ± 9 | 408 ± 8 |

| Metabolic study (14 weeks post-lesion) |  |
| Sodium intake (mmol/kg body wt.) | 57 ± 11 | 46 ± 5 | 55 ± 9 | 51 ± 11 |
| Na excretion (mmol/kg body wt.) | 58 ± 11 | 39 ± 12 | 60 ± 4 | 47 ± 11 |
| Plasma sodium (mmol/l) | 141 ± 3 ± 0 | 142 ± 8 ± 0 | 142 ± 4 ± 1 | 142 ± 0 ± 1 |

Results are shown as means ± SEM. For blood pressure and heart rates, results are the means of six measurements taken over a 24 h span. * indicates a significant difference from control group of same strain; N.S., not significant. DSS, Dahl salt-sensitive sham-operated; DSLE, Dahl salt-sensitive effective lesion; DRS, Dahl salt-resistant sham-operated; DRLE, Dahl salt-resistant effective lesion. Numbers in parentheses refer to numbers of animals.
lesions selectively decrease aldosterone production [11]. (2) Both PVN and SCN have large amounts of vasopressin and neurophysin [12]; there is a SCN projection to the nucleus tractus solitarius; in addition, the PVN and PVE have projections to the sympathetic neurons in the spinal cord [8]; vasopressin influences catecholamine turnover in the nucleus tractus solitarius [13]; further, the presence of vasopressin–neurophysin fibres in the region of this nucleus and the dorsal motor nucleus of the vagus suggests that vasopressin may act at yet another level to modulate ACTH secretion. These two regions are involved in the reflex release of ACTH in response to haemodynamic stimuli arising from atrial stretch and carotid baroreceptors. (3) The anteromedial hypothalamus may participate in other aspects of endocrine and autonomic control relevant to hypertension [8].

Future studies are needed to determine the relative contributions of different mechanisms to the antihypertensive effects we observed in our study.

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References


