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# SHORT COMMUNICATION

# THE HYPERTENSINOGENIC ACTIVITY OF 19-NOR-DEOXYCORTICOSTERONE IN THE ADRENALECTOMIZED SPONTANEOUSLY HYPERTENSIVE RAT

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**Summary**—Infusions of 10 or 25 μg/day 19-nor-DOC for 2 weeks in adrenalectomized spontaneously hypertensive rats led to significant increases in blood pressure, 55 and 70 mmHg respectively. This study provides further evidence that 19-nor-DOC is a potent hypertensinogenic steroid and that the ADX SHR model is a useful, sensitive bioassay system to test for hypertensinogenic activity.

## INTRODUCTION

19-nor-Deoxycorticosterone (19-nor-DOC) is a very potent mineralocorticoid when tested for electrolyte changes in both rat and isolated toad bladder assay systems [1, 2]. This steroid was isolated from the urine of rats with adrenal regeneration hypertension [3] and has been shown to increase blood pressure (BP) in the uni-nephrectomized salt-loaded rat [4]. It is also present in increased levels in the urine of patients with low renin hypertension [5, 6]. In addition, increased urinary excretion of 19-nor-DOC has been reported in young, spontaneously hypertensive rats (SHR) prior to the development of their hypertension [7].

We have previously reported that adrenalectomy (ADX) inhibits the development of hypertension in young SHR and that infusions of small dosages of the mineralocorticoid, aldosterone (2 and 10 μg/day) markedly increases the blood pressure of ADX SHR to hypertensive levels (> 150 mmHg) [8]. The effects of infusions of 19-nor-DOC were therefore investigated in ADX SHR to determine the hypertensinogenic activity of the steroid.

## EXPERIMENTAL

Male SHR (Charles River Breeding Laboratories) were maintained on Purina Rat Chow and tap water *ad libitum* under constant conditions of a 12 h light–dark cycle and a room temperature of 22°C.

At 6 weeks of age, rats were divided into groups ($n = 4$) and were bilaterally adrenalectomized under ether anesthesia. Each rat received a s.c. implant of a constant infusion pump (Model 2002, Alza Corp.). Pumps were loaded with either 19-nor-DOC in propylene glycol to deliver 2, 10 or 25 μg/day or propylene glycol only (sham pumps). The 19-nor-DOC was generously provided by Dr C. E. Gomez-Sanchez, Veterans Administration Hospital (Tampa, FL). Thereafter all rats were maintained with 0.9% NaCl as drinking water *ad libitum*.

Prior to surgery, and every 3 days thereafter, the rats were weighed and systolic BP was measured by the indirect tail cuff method between 10 am and noon. BP was measured using an electrosphygomanometer and pneumatic pulse transducer (Narco Biosystems, Houston, TX) and was determined by the mean of three measurements.

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At the end of the experimental period (2 weeks) the rats were anesthetized with ether and blood samples were withdrawn from the aorta into vacutainer tubes containing EDTA. Plasma was stored −20°C for later analysis.

Plasma renin activity (PRA) was measured by radioimmunoassay (RIA; New England Nuclear) of generated angiotensin I [9].

Paired and unpaired data were compared statistically by Student's *t*-test.

## RESULTS

During the 2-week experimental period, the BP of control ADX SHR given sham mini-osmotic pumps did not change significantly from initial values measured prior to adrenalectomy (115 ± 3.4 mmHg mean ± SEM; Fig. 1). Infusion of 25 μg 19-nor-DOC per day, however, resulted in a significant elevation in the BP of ADX SHR ($P < 0.05$) after 6 days. Their BP continued to rise during the remainder of the 2-week period, reaching a final value of 187 ± 15 mmHg, which was approx. 70 mmHg higher than initial values. Rats receiving 10 μg 19-nor-DOC per day for 14 days also showed a significant elevation in BP of approx. 55 mmHg ($P < 0.05$), but little or no change in BP occurred among the rats given 2 μg 19-nor-DOC per day. Each group of rats showed a similar increase in body weight (~ 55 g) during the 2-week period.

Infusions of 10 and 25 μg 19-nor-DOC per day also led to a significant decrease ($P < 0.05$) in PRA levels (3.03 ± 3.25 and 0.42 ± 0.16 ng/ml/h, respectively) after 2 weeks compared to those of the control rats (45.0 ± 14.2 ng/ml/h). The PRA level of rats receiving the lower dosage (2 μg per day) of 19-nor-DOC also showed a small decline (35.26 ± 17.41 ng/ml/h).

## DISCUSSION

Considerable interest has been given recently to the role of 19-nor-steroids in hypertension following the isolation by Gomez-Sanchez *et al.* of 19-nor-DOC from the urine of rats with adrenal regeneration hypertension [3]. Although several of these steroids were synthesized at least 20 years ago [2, 10, 11], other new 19-OH- and 19-nor-compounds have recently been synthesized both enzymatically and chemically, promising continued and further interest in these unique derivatives of steroid hormones [12–14].

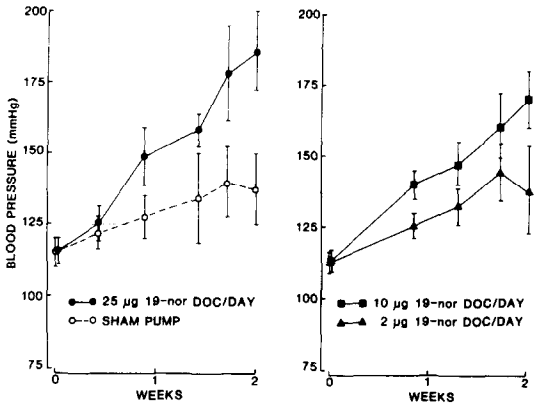


Fig. 1. The effects of infusions of 19-nor-DOC (2, 10 and 25 $\mu$g/day) on the blood pressure of ADX SHR. Values are the mean $\pm$ SE ($n = 4$).

Aoki demonstrated several years ago that the development of hypertension in young SHR required the presence of several endocrine glands, including the adrenal [15]. Our laboratories have recently reported that the inhibition of development of hypertension in young SHR caused by adrenalectomy could be reversed by infusions of low dosages of aldosterone (2 and 10 $\mu$g/day). Although several investigators have also suggested the adrenal gland participates in the development of hypertension in SHR [16–18], others have disputed any role for either the adrenal gland or the renin–angiotensin system in this rat. The present study indicates that 19-nor-DOC can cause significant increases in BP in young ADX SHR. This occurs at dosages approx. 10–25 times larger than those reported for aldosterone. The completely suppressed PRA of ADX SHR receiving the highest dosage of 19-nor-DOC also reflects their responsiveness to this potent mineralocorticoid. Together, these results suggest that the ADX SHR model is very sensitive and can be useful for the screening of suspected hypertensinogenic steroids.

Young SHR have been shown to have elevated urinary levels of 19-nor-DOC [7] and some investigators have demonstrated that plasma levels of aldosterone are increased in SHR [16–18]. We realize, however, that the present studies, together with our previous experiments [8, 19], do not yet constitute evidence that any particular endogenous mineralocorticoid necessarily causes the rise of BP in young SHR. Rather, these experiments only demonstrate the efficacy of this rat model for screening potential hypertensinogenic steroids and lay the groundwork for further experiments detailing the putative role of adrenal steroids in the development of hypertension in SHR.

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