The Role of Hypothalamo-sympathetic Nerve System to Maintain High Blood Pressure in DOCA Hypertensive Rats

KAZUO TAKEDA, SUSUMU SASAKI, ISAO KAIMASU, MANABU YOSHIMURA, MASAO NAKAGAWA, HAMAO IJICHI, RUBEN D. BUNAG*

DOCA/SALINE induced hypertension in rats has been contributed to the research of hypertension as well as spontaneously hypertensive rats (SHR). However, the mechanism of hypertension is not yet clear. In order to determine whether sympathetic overactivity exists and participate in DOCA hypertension, sympathetic nerve activity was directly recorded in DOCA hypertensive rats and additionally investigated the mechanism to keep high blood pressure in DOCA hypertension. After left nephrectomy, silicicon rubber molds containing desoxycorticosterone acetate (DOCA, 200 mg/kg) were implanted subcutaneously in sprague dawley rats, while silicicon rubber mold alone were implanted as the control.

Saline was administrated instead of drinking water, and systolic pressure and heart rate were measured weekly by tail cuff method. About two months later, these rats were used for acute experiment. Coaxial electrode was implanted in the posterior hypothalamus with standard stereotaxic technique. Hypothalamus was stimulated electrically with 1 msec pulse width, 100/sec frequency for 10 sec with 50, 100 and 200 μA current strength.

All rats were anesthetized with urethane (1.0 g/kg) during acute experiment. Iliac artery and jugular vein were cannulated to record blood pressure and inject some drugs, respectively.

Sympathetic nerve signals were recorded with bipolar electrode at major bundle just below coeliac ganglion before and during hypothalamic stimulation. Sympathetic nerve activity was analyzed following previously reported method. (Takeda K and Bunag DR, J. Clin. Invest. 62: 642-648, 1978.)

Fig.1. Effect of hypothalamic stimulation on sympathetic nerve activity and mean aortic pressure in control (dotted line) and DOCA hypertensive (solid line) rats. Successive points for each rat group represent average + SEM increases (nerve activity expressed as the number of spikes in first three second during stimulation) produced by stimulation with 50, 100 and 200 μA currents, respectively.

Key Words:
DOCA hypertension
Sympathetic nerve
Hypothalamus

Second Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, 602 Japan
* The University of Kansas Medical Center, Kansas 66103, U.S.A.

Norepinephrine was injected to examine pressor responses in all rats and pentolinium also injected routinely. After finishing all recordings, the position of electrode was examined by sectioning the brain.

Two months later after implantation of DOCA mold, systolic pressure was significantly higher in DOCA treated rats than in control (159 ± 9, 119 ± 4 mmHg; p < 0.001), while heart rate and body weight were not different between two groups. In anesthetized rats, mean blood pressure was also higher in DOCA treated rats than in control (140 ± 7, 112 ± 2; p < 0.001). Similarly, basal sympathetic nerve activity was significantly larger in DOCA hypertensive rats. (74 ± 9, 52 ± 5 spikes/3 sec; p < 0.05). Pressor responses to injected norepinephrine were significantly larger in DOCA hypertensive rats than in control at any doses (e.g. 22 ± 4, 9 ± 1 mmHg at 100 ng/100g; p < 0.005). And also similar results were obtained in pressor responses to hypothalamic stimulation (e.g. 40 ± 4, 15 ± 2 at 100 μA; p < 0.005). Increases of sympathetic nerve spikes during hypothalamic stimulation were also significantly larger in DOCA hypertensive rats than those in control. Pressor and sympathetic nerve responses to hypothalamic stimulation were summarized in the figure.

The line of DOCA hypertensive rats shifted to right from the line of control, it means pressor responsiveness is enhanced in DOCA treated rats. And also it shifted up from control, which means the enhanced responses of sympathetic nerve activity to electrically hypothalamic stimulation. Vasodepression by ganglionic blockade (pentolinium) was significantly larger in DOCA hypertensive than in control rats (78 ± 6, 53 ± 3; p < 0.005).

These results suggest that hypothalamic-sympathetic hyperactivity contributes to maintain high blood pressure in DOCA hypertensive rats, as well as vascular hyperresponsiveness does.