

## **Inhibition of Abnormal Hindquarter Vascular Tone in Spontaneously Hypertensive Rats with Chlorpromazine**

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IRIUCHIJIMA, J. *Inhibition of Abnormal Hindquarter Vascular Tone in Spontaneously Hypertensive Rats with Chlorpromazine.* Tohoku J. Exp. Med., 2000, **192** (1), 35-40 ——— The presence of an abnormal sympathetic vascular tone is assumed in the hindquarters of spontaneously hypertensive rats (SHR) on the basis that ganglionic blockade decreases hindquarter vascular resistance (HQR) in them but not in normotensive control rats (NCR). Hindquarter blood flow (HQF) was observed with an electromagnetic flow probe implanted around the terminal aorta in SHR and NCR in the conscious state. Mean arterial pressure (AP) was also recorded with an indwelling catheter. HQR was calculated as AP divided by HQF. Intravenous bolus injection of chlorpromazine-HCl at 0.5 mg/kg significantly decreased HQR in SHR but not in NCR. Thereafter, in SHR, ganglionic blockade with hexamethonium bromide did not decrease HQR further. Chlorpromazine given to SHR after ganglionic blockade did not decrease HQR either. These findings indicate that the abnormal hindquarter tone in SHR was inhibited by chlorpromazine. It is suggested that dopaminergic neurons are involved in the hindquarter sympathetic tone generation. ——— hindquarter flow; SHR; chlorpromazine; sympathetic tone © 2000 Tohoku University Medical Press

In spontaneously hypertensive rats (SHR; Okamoto and Aoki 1963) ganglionic blockade significantly decreases hindquarter vascular resistance but not in normotensive control rats (NCR) (Iriuchijima 1985, 1988). On the basis of this finding we assume an abnormal sympathetic tone in the hindquarter vascular area of SHR. The tone is responsible for more than half of the decreased total peripheral conductance (inverse of total peripheral resistance) in this type of rat hypertension (Iriuchijima 1985). The supraspinal origin of the tone was assessed since it was abolished after high spinal transection (Iriuchijima 1992).

We have been trying to find chemicals which inhibit the supraspinal tone generation in SHR. Clonidine, which is thought to inhibit sympathetic tone

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(Schmitt and Schmitt 1969; Kobinger 1978; Hieble and Kolpak 1993; Wang et al. 1994), was found ineffective (Iriuchijima 1997). The present study reports that chlorpromazine is one which fulfills the above requirement.

## METHODS

### *Rats*

A total of 22 SHR and 5 NCR were used in this study. They were all obtained from the Japan Charles River Co. (Yokohama).

### *Implantation*

Under anesthesia with thiamylal sodium (50 mg/kg, i.p.), an electromagnetic flow probe (type FC, Nihon Kohden, Tokyo) with an internal diameter of 1.5 or 2 mm was implanted around the terminal aorta for hindquarter blood flow (HQF). For observation of mean arterial pressure (AP) an indwelling catheter was placed in the right common carotid. Another catheter was inserted into the right external jugular vein for intravenous injection.

The wire with a plug from the flow probe and the catheter ends were passed subcutaneously and exteriorized at the dorsal neck.

### *Recording*

After implantation, each rat was kept separately in a white 35×37×17 cm polyethylene cage containing wood chips. Water and food pellets were given ad libitum. Two to 4 days after implantation, after the rat had resumed eating and drinking, the cable from the flowmeter circuit (MFV-3100, Nihon Kohden) was connected to the plug of the flow probe. The polyethylene tube from a pressure transducer was connected to the arterial catheter. Pressure and flow signals were smoothed with an RC (resistance-capacitance) low pass filter with a time constant of 1 second and recorded with a rectangular pen-writer.

### *Statistics*

Statistical analysis was performed by analysis of variance (ANOVA): where  $p < 0.05$  was found, further analysis by the paired  $t$ -test was performed.

## RESULTS

### *Effects of chlorpromazine*

Fig. 1 reproduces the recording of AP and HQF in an SHR. At the arrow 0.5 mg/kg of chlorpromazine-HCl was injected intravenously. Injection induced a marked decrease in AP extending over 20 minutes but HQF remained almost unchanged except for an acute, brief increase immediately after injection. Hindquarter resistance (HQR) calculated as AP/HQF was decreased.

Fig. 2 summarizes the data for the above experiment which was performed in 8 SHR and 5 NCR. Two way ANOVA revealed that chlorpromazine significantly

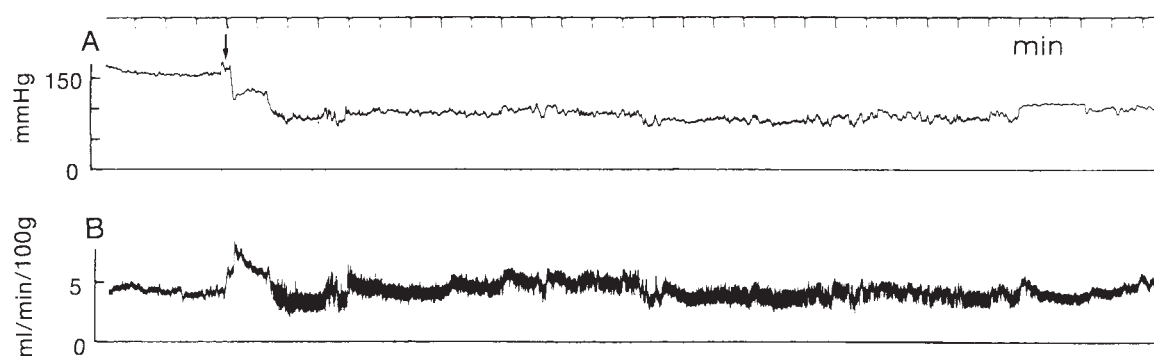


Fig. 1. Simultaneous recording of arterial pressure (AP) and hindquarter (terminal aortic) flow (HQF) in a conscious female SHR (190 g, 13 week-old). At the arrow 0.5 mg/kg of chlorpromazine was injected intravenously. Injection induced a marked decrease in AP continuing over 30 minutes. HQF remained almost unchanged except an initial brief increase. HQF was decreased.

decreased AP in both SHR and NCR (both  $p < 0.01$ ) but HQF only in SHR ( $p < 0.05$ ).

From Fig. 2 we conclude that the time point of 10 minutes after injection was suitable for comparison of the variables with the premedication control values. The paired  $t$ -test for the values 10 minutes after injection in comparison with the premedication controls revealed that AP was significantly lower in both SHR ( $p < 0.01$ ) and NCR ( $p < 0.025$ ) but HQF only in SHR ( $p < 0.01$ ).

The SHR group in the above experiment consisted of 5 males and 3 females, while all 5 rats were male in the NCR group. However, this inequality of sex ratio between groups did not seem to affect the conclusion: even with the 5 males alone of the SHR group, by ANOVA AP and HQF were significantly decreased after chlorpromazine ( $p < 0.01$  for both AP and HQF) and, in comparison with the premedication values by the  $t$ -test, AP was significantly decreased 10 minutes after injection at  $p < 0.01$  and HQF at  $p < 0.05$ .

A similar but slightly more intense effect was obtained with a double dose (1 mg/kg) in another group of 5 SHR (3 males and 2 females). In two more SHR (one male and one female) a half dose (0.25 mg/kg) was tried, which gave obviously smaller effects than those at 0.5 mg/kg. Thus it appears that the dose of 0.5 mg/kg is appropriate for our purpose in examining the inhibitory effect of chlorpromazine on the hindquarter tone.

#### *Ganglionic blockade after chlorpromazine*

In 7 (5 males and 2 females) of the 8 SHR and all 5 NCR used in the experiment summarized in Fig. 2, a 2.5% (w/v) solution of hexamethonium bromide (C6) was infused at a rate of 0.8 mg/min for a total dose of 25 mg/kg for ganglionic blockade. Infusion was started about 30 minutes after chlorpromazine injection.

AP, HQF, and HQR were compared before and after blockade (Fig. 3). In

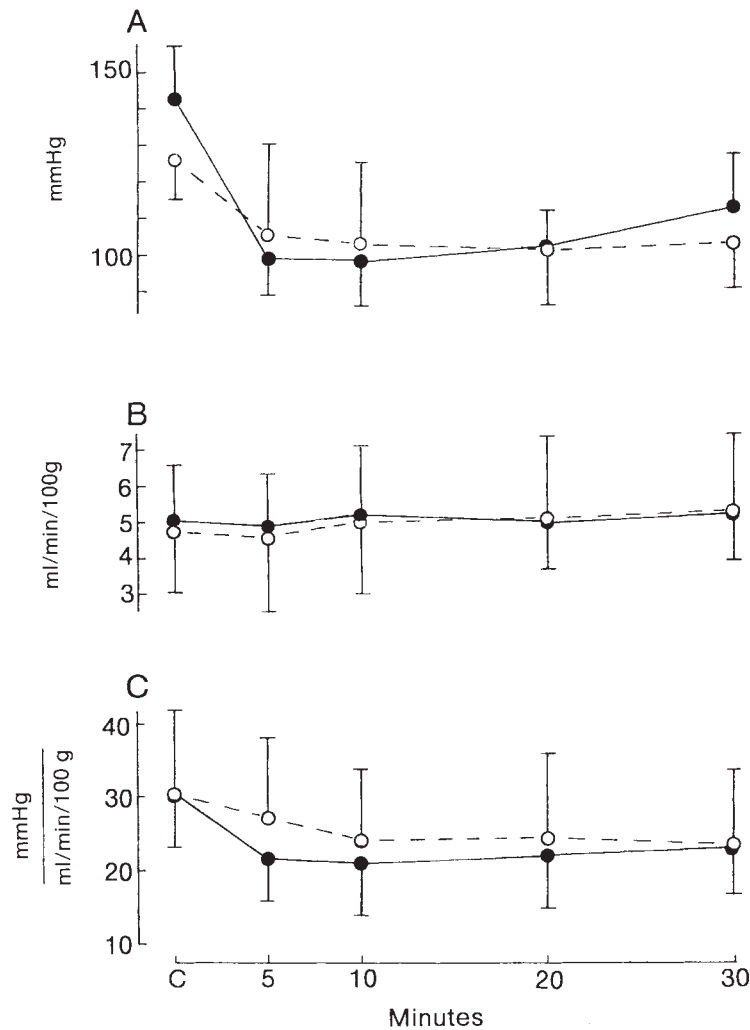


Fig. 2. Mean  $\pm$  s.d. of arterial pressure (A), hindquarter flow (B), and hindquarter resistance (C) from 8 SHR (filled circles) (5 males and 3 females) ( $210 \pm 33$  g,  $12.5 \pm 3.2$  week-old) and 5 male NCR (open circles) ( $424 \pm 64$  g,  $15.4 \pm 3.2$  week-old) before and after bolus intravenous injection of chlorpromazine at 0.5 mg/kg. By two way ANOVA, AP was decreased significantly in both SHR and NCR (both  $p < 0.01$ ) but HQR only in SHR ( $p < 0.05$ ).

both groups AP was significantly decreased ( $p < 0.001$  by the paired  $t$ -test) but HQF and HQR were not.

#### *Chlorpromazine after ganglionic blockade*

In another group of 7 SHR (5 males and 2 females), first ganglionic blockade was performed and thereafter chlorpromazine (0.5 mg/kg) was injected. The mean  $\pm$  s.d. of the variables before and after blockade as well as 10 minutes after chlorpromazine are plotted in Fig. 4. The two way ANOVA revealed significant effects on AP ( $p < 0.01$ ) and HQR ( $p < 0.05$ ) but not on HQF. Chlorpromazine injection significantly decreased AP ( $p < 0.01$  by the paired  $t$ -test) but not HQR.

#### DISCUSSION

The  $D_2$ -dopamine blocker chlorpromazine significantly decreased HQR in

SHR but not in NCR (Fig. 2). Ganglionic blockade which should decrease HQR in SHR without preceding chlorpromazine (Iriuchijima 1985, 1988) did not decrease HQR further after chlorpromazine (Fig. 3). One might suppose that the same result should be obtained if chlorpromazine had inhibitory effects on such peripheral tissues as vascular smooth muscle. However, we believe this to be unlikely because chlorpromazine had no effect on HQR after ganglionic blockade (Fig. 4).

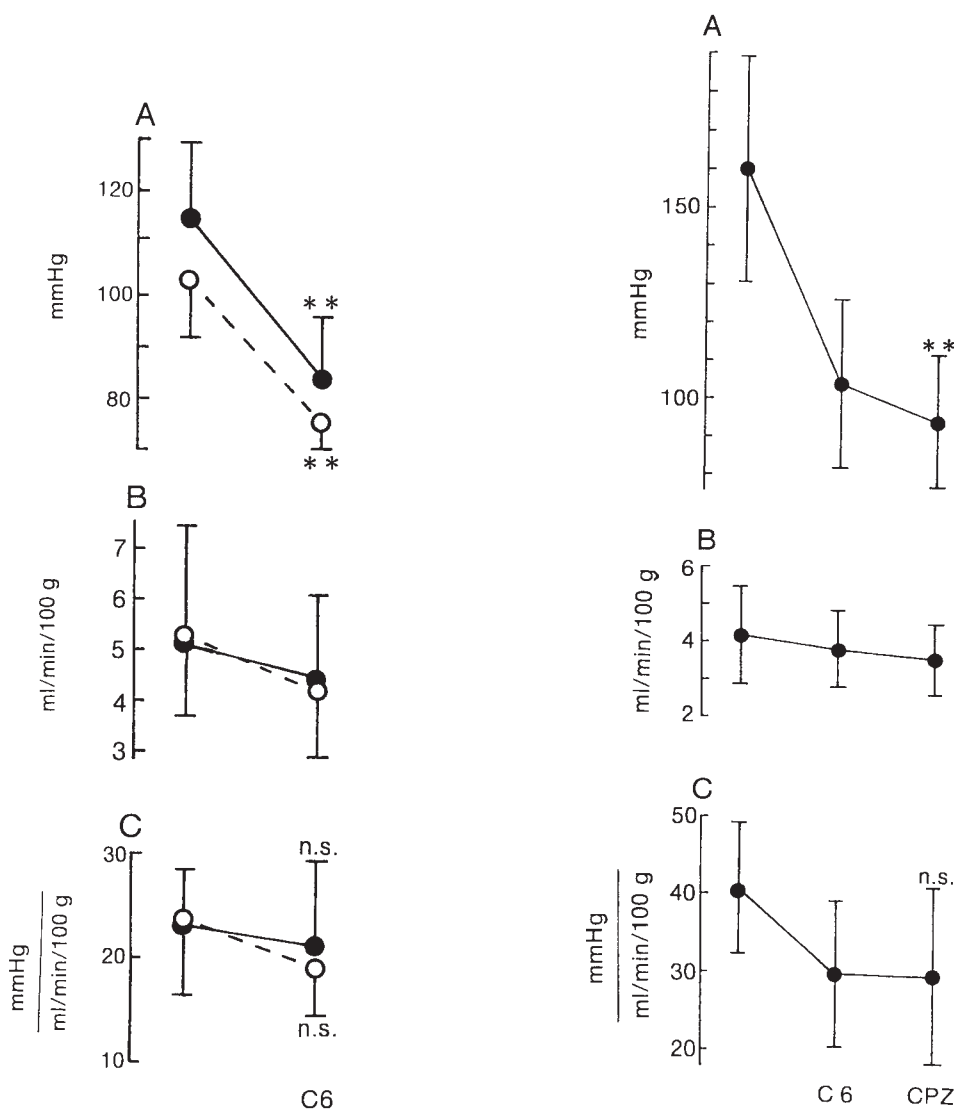


Fig. 3. Mean  $\pm$  s.d. of arterial pressure (A), hindquarter flow (B), and hindquarter resistance (C) from 7 SHR (filled circle) and 5 NCR (open circles) before and after ganglionic blockade with hexamethonium bromide (C6) (25 mg/kg). About 30 minutes before blockade, chlorpromazine (0.5 mg/kg) was injected. \*\* $p < 0.01$ ; n.s., not significant.

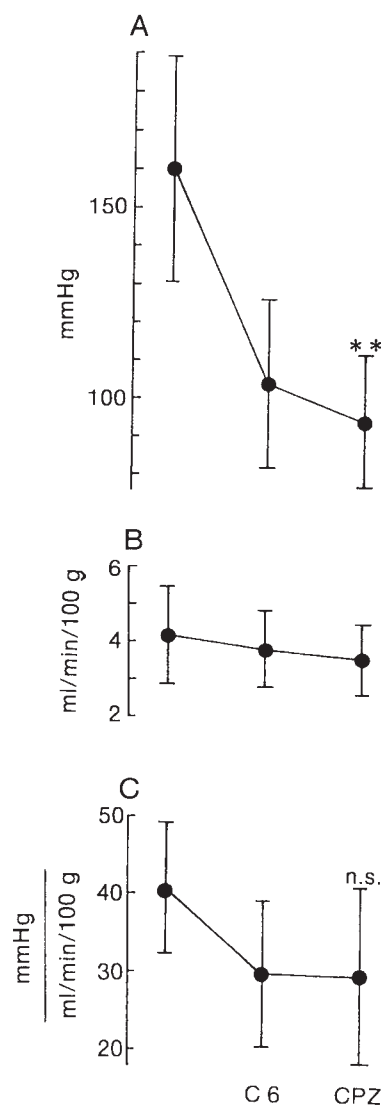


Fig. 4. Successive changes of arterial pressure (A), hindquarter flow (B), and hindquarter resistance (C), each mean  $\pm$  s.d., in 7 SHR (5 males and 2 females) (234  $\pm$  33 g, 13.0  $\pm$  2.7 week-old) before administration, after ganglionic blockade (C6), and 10 minutes after chlorpromazine (0.5 mg) (CPZ). \*\*significant change at  $p < 0.01$  by the paired  $t$ -test on chlorpromazine; n.s., not significant.

These findings indicate that chlorpromazine inhibits the abnormal hindquarter sympathetic tone in SHR and suggest that dopaminergic neurons take part in the generation of the tone.

Although ganglionic blockade with hexamethonium after chlorpromazine did not decrease HQR, it did decrease AP significantly in both SHR and NCR (Fig. 3). This suggests that sympathetic tone remains in some vascular areas other than the hindquarters after chlorpromazine administration. It is also suggested that the competitive  $\alpha$ -adrenergic blocking action of chlorpromazine observed in vitro (Goodman and Gilman 1970) is imperfect, if present at all, at the dose and under the condition employed in this study.

In summary, chlorpromazine inhibited the abnormal hindquarter tone in SHR, suggesting involvement of dopaminergic neurons in generation of the tone.

#### References

- 1) Goodman, L.S. & Gilman, A. (1970) *The Pharmacological Basis of Therapeutics*, 14th ed., MacMillan, London, p. 561
- 2) Hieble, J.P. & Kolpak, D.C. (1993) Mediation of the hypotensive action of systemic clonidine in the rat by  $\alpha_2$ -adrenoceptors. *Br. J. Pharmacol.*, **110**, 1635-1639.
- 3) Iriuchijima, J. (1985) Mechanism of elevation of hindquarter vascular resistance in spontaneously hypertensive rats. *Jpn. J. Physiol.*, **35**, 45-56.
- 4) Iriuchijima, J. (1988) Abnormal hindquarter vasoconstrictor tone, a feature common to various kinds of hypertensive rats. *Jpn. J. Physiol.*, **38**, 545-548.
- 5) Iriuchijima, J. (1992) Supraspinal origin of abnormal hindquarter vasoconstrictor tone in spontaneously hypertensive rats. *Tohoku J. Exp. Med.*, **167**, 115-119.
- 6) Iriuchijima, J. (1997) Why is the hypotensive effects of clonidine greater in hypertensive rats? *Tohoku J. Exp. Med.*, **182**, 271-276.
- 7) Kobinger, W. (1978) Central  $\alpha$ -adrenergic systems as targets for hypotensive drugs. *Rev. Physiol. Biochem. Pharmacol.*, **81**, 39-100.
- 8) Okamoto, K. & Aoki, K. (1963) Development of a strain of spontaneously hypertensive rats. *Jpn. Circul. J.*, **27**, 282-293.
- 9) Schmitt, H. & Schmitt, H. (1969) Localization of the hypotensive effect of 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride (St. 155, Catapressan). *Eur. J. Pharmacol.*, **6**, 8-12.
- 10) Wang, C., Knowles, M.G., Chakrabarti, M.K., & Whitwam, J.G. (1994) Clonidine has comparable effects on spontaneous sympathetic activity and afferent A $\delta$ - and C-fiber-mediated somatosympathetic reflexes in dogs. *Anesthesiology*, **81**, 710-717.