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Why is the Hypotensive Effect of Clonidine Greater in Hypertensive Rats?

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IRIUCHIJIMA, J. *Why is the Hypotensive Effect of Clonidine Greater in Hypertensive Rats?* Tohoku J. Exp. Med., 1997, **182** (4), 271-276 —— The original aim of this study was to observe whether the depressor drug clonidine inhibited the abnormal hindquarter tone in spontaneously hypertensive rats (SHR). In conscious SHR and normotensive control rats (NCR), hindquarter (terminal aortic) blood flow was observed with an implantd electromagnetic flow probe and mean arterial pressure with an indwelling catheter. Twenty minutes after intravenous injection of clonidine (5 μg/kg) when arterial pressure reached a steady lower level, hindquarter resistance (HQR), calculated as mean arterial pressure divided by hindquarter flow, did not decrease in SHR. Thus we were unable to obtain evidence for an inhibitory effect of clonidine on the abnormal hindquarter tone in SHR. In NCR, HQR increased significantly by clonidine. The decrease in arterial pressure on clonidine was greater in SHR than in NCR, presumably because the increase in HQR partially offset the hypotensive effect in NCR. It seems that the increase in HQR in NCR was induced by a reflexive excitation of regional sympathetic vasoconstrictor fibers, which, being the final common path for the abnormal hindquarter tone also, were already being excited in SHR before clonidine administration. This point was quantitatively verified. ——— clonidine; SHR; hindquarter vascular resistance

A substantial part of the hypertension in spontaneously hypertensive rats (SHR)(Okamoto and Aoki 1963) is sustained by the abnormal sympathetic vasoconstrictor tone in the hindquarters (Iriuchijima 1985, 1988). The tone is considered as being generated at the supraspinal level, because it is abolished by high spinal transection (Iriuchijima 1992).

Clonidine, an α_2-adrenergic receptor agonist, is thought to decrease blood pressure by causing a reduced sympathetic nerve firing rate with the locus of its action within the CNS (Schmitt and Schmitt 1969; Kobinger 1978; Hieble and Kolpak 1993). The present study was undertaken to determine whether the abnormal hindquarter tone in SHR is inhibited by clonidine.

Contrary to expectation, we were unable to obtain evidence for an inhibitory effect of clonidine on the abnormal hindquarter tone, because it did not decrease the hindquarter resistance (HQR) in SHR. However, comparison of the effect of

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clonidine on HQR between SHR and normotensive control rats (NCR) seems to have given an answer to the question why this drug has a greater hypotensive effect in SHR than in NCR.

Methods

SHR used in this study were descendants from those donated from the Shimane Medical College. NCR were Wistar rats obtained from a local distributor. Mean arterial pressure was observed with an indwelling catheter placed either in the terminal aorta or common carotid. For recording hindquarter (terminal aortic) flow, 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. Another catheter was inserted into the right external jugular vein for intravenous drug injection. The operation was performed under anesthesia with thiamylal sodium (50 mg/kg, i.p.). The wire with a plug from the probe and the catheter ends, filled with heparinized saline (10 U of heparin/ml) and plugged with a short piece of stainless steel wire, were tunneled subcutaneously to exit between the scapulae.

After implantation, each rat was kept separately in a white $35 \times 37 \times 17$ cm polyethylene cage containing wood chips. Water and food pellets were given ad libitum. Two to four days after implantation, the polyethylene tube from a pressure transducer was connected to the arterial catheter and the cable from the flowmeter circuit (MFV-1100; Nihon Kohden) to the plug of the flow probe. Pressure and flow were recorded with a rectangular pen-writer.

Results

Dose of clonidine and time point after dosage when drug effect was mainly observed

As a preliminary experiment, the time course of blood pressure after a bolus i.v. injection of clonidine at doses 2-10 μg/kg body weight was observed. After several trials a dose of 5 μg/kg was selected as appropriate for studying the depressor effect of this drug: At this dose, in both SHR and NCR, the depressor effect seemed to be greater than that at 2 μg/kg but comparable with that at 10 μg/kg. The successive change in mean arterial pressure after this dose of clonidine in SHR and NCR is presented in Fig. 1. It may be said that this figure as a whole shows that the hypotensive effect was greater in SHR than in NCR.

In both groups of rats, the pressure reached a new lower plateau level in 20 minutes. Therefore, variables 20 minutes after a bolus injection of 5 μg/kg of clonidine were dealt with as representative ones under the effect of the drug. At this time point after this dose, arterial pressure was significantly lower than the predrug level at $p < 0.01$ for SHR and at $p < 0.001$ for NCR by the paired t-test. The mean decrease $\pm$ S.D. was -18.4 ± 12.2 mmHg for SHR ($n = 9$) and -11.1 ± 5.2 mmHg for NCR ($n = 11$).

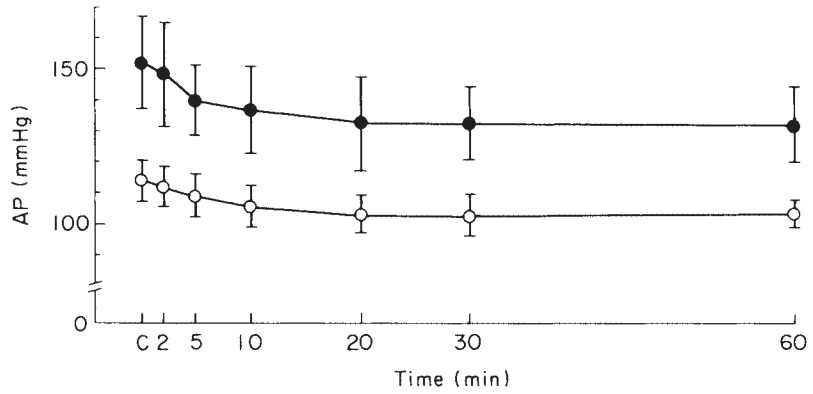

Fig. 1. Time course of decrease in blood pressure after injection of 5 μg/kg of clonidine. Filled circles: SHR ($n=9$, 231 ± 11 g, 13 ± 1 w.o.), open circles: NCR ($n=11$, 292 ± 89 g, 13 ± 2 w.o.). Note that, in both SHR and NCR, a new plateau level had been reached in 20 minutes. Twenty minutes after injection blood pressure was significantly lower than the control at $p<0.01$ for SHR and $p<0.001$ for NCR. C, predrug control value.

Effects of clonidine on hindquarter flow and resistance

Fig. 2 shows one example of recording of arterial pressure and hindquarter flow in an SHR and NCR before and after bolus injection of clonidine at 5 μg/kg. A difference to note between the SHR and NCR was that, after injection, HQF markedly decreased in the NCR but not in the SHR.

Fig. 3 summarizes the results from 6 SHR and 8 NCR. HQF decreased and HQR increased significantly in NCR ($p<0.01$ for HQF and 0.05 for HQR by the paired t-test) but not in SHR.

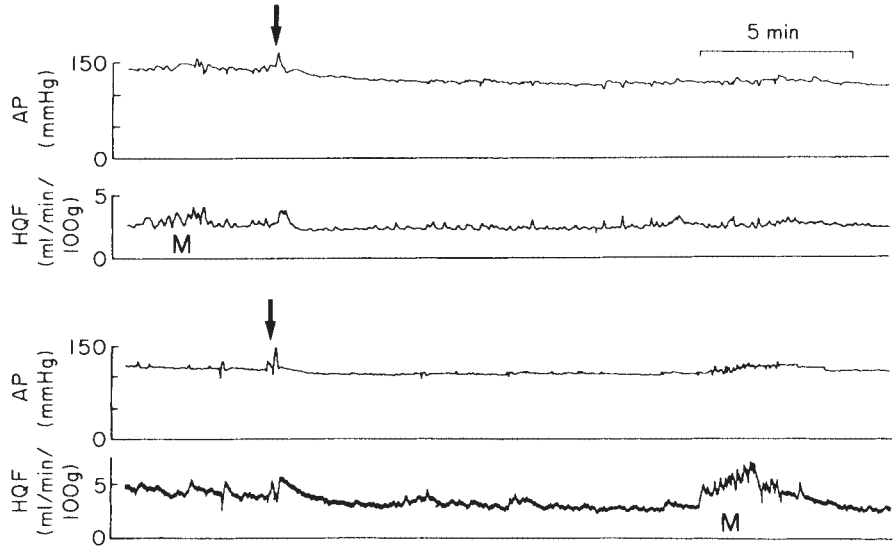

Fig. 2. Effects of clonidine (5 μg/kg, i.v., at the arrow) on arterial pressure (AP) and hindquarter flow (HQF). Upper pair: SHR, 240 g, 12 w.o.; Lower pair: NCR, 345 g, 12 w.o. Note the marked decrease in HQF in NCR. Around M the rat was excited and moving in the cage, causing a marked increase in HQF.

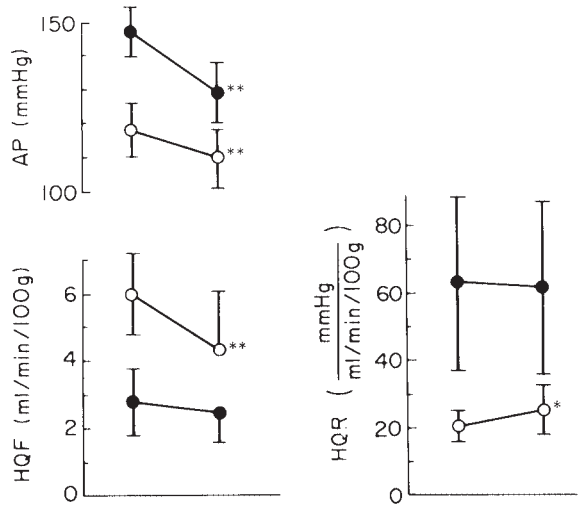

Fig. 3. Mean±S.D. of AP, HQF, and HQR from 6 SHR (252±23 g, 15±3 w.o.) (filled circles) and 8 NCR (290±23 g, 13±2 w.o.) (open circles), before and 20 minutes after clonidine (5 μg/kg, i.v.). Only in NCR, HQF decreased and HQR increased significantly. $^{*}p<0.05$, $^{**}p<0.01$ by the paired t-test.

Discussion

Since clonidine is a depressor drug acting on the CNS (Schmitt and Schmitt 1969; Kobinger 1978; Hieble and Kolpak 1993) and since the major contribution to hypertension in SHR is abnormal sympathetic tone in the hindquarters (Iriuchijima 1985, 1988), it was expected that the drug decreased HQR in SHR. In reality, however, clonidine did not decrease HQR in SHR 20 minutes after a bolus injection of 5 μg/kg, when arterial pressure decreased significantly. In other words, we were unable to obtain evidence for inhibition of the abnormal hindquarter tone in SHR by clonidine.

Clonidine significantly increased HQR in NCR when the arterial pressure decreased. Previously, we have reported that such hypotensive agents as pentobarbital and the nitrate molsidomine increase HQR of NCR, which is ascribable to a reflex excitation of regional sympathetic vasoconstrictor fibers (Teranishi and Iriuchijima 1992, 1994). We have coined the term 'hindquarter compensator' to describe the function of HQR compensating for hypotension. The observed increase in HQR in NCR in response to clonidine injection may be interpreted as an activation of the hindquarter compensator. We consider that the hypotensive effect of clonidine is more marked in SHR than in NCR because the ability of the hindquarter compensator is encroached upon by the presence of the abnormal hindquarter tone (Iriuchijima 1985, 1988).

The following calculation was done to examine whether the above qualitative consideration has a quantitative basis.

If we denote mean arterial pressure as P, total peripheral resistance as R, and cardiac output as Q, it may be written

$$P = RQ. \tag{1}$$

Using total conductance G, which is the inverse of R,

$$P = Q/G. \tag{2}$$

If we denote the hindquarter conductance as g and the conductance of the whole remaining body as G',

$$G = g + G'. \tag{3}$$

Substituting (2) with (3), we have

$$P = Q/(g + G'). \tag{4}$$

By partial differentiation with respect to g,

$$\partial P/\partial g = -Q/(g+G')^2 \tag{5}$$

or

$$\partial P/\partial g = -Q/G^2 = -P^2/Q. \tag{6}$$

Since the mean arterial pressure (P) in NCR is about 110 mmHg on the average and the cardiac output (Q) 22 ml/min/100 g body weight (Iriuchijima et al. 1980), substituting (6) with the above,

$$\partial P/\partial g = -550 \text{ mmHg}/((\text{ml/min})/\text{mmHg}). \tag{7}$$

Or, approximately,

$$\Delta P/\Delta g = -550 \text{ mmHg}/((\text{ml/min})/\text{mmHg}). \tag{8}$$

As seen from Fig. 3, clonidine increased the average HQR in NCR from about 20 to 25 mmHg/(ml/min). The average g, hindquarter conductance or inverse of HQR, decreased from about 0.05 to 0.04 (ml/min)/mmHg. Therefore, $\Delta g = -0.01$ mmHg/(ml/min).

Substituting (8) with this value, we obtain

$$\Delta P = 5.5 \text{ mmHg}.$$

This result indicates that the observed change in HQR on clonidine administration, if other variables remained unchanged, would increase arterial pressure by about 6 mmHg. This is comparable to the difference in the observed decrease in arterial pressure by clonidine between SHR and NCR (-18 ± 12.2 mmHg vs. -11.1 ± 5.2 mmHg). Remembering that HQR was almost unchanged in SHR by clonidine, we may say that our hypothesis that the increase in HQR in NCR on clonidine administration offsets its hypotensive effect is quantitatively tenable.

In summary, our results and calculation suggest that clonidine was more hypotensive in spontaneously hypertensive rats than in normal rats because sympathetic vasoconstrictor fibers that compensate for the hypotensive effect of clonidine are already in action in the former.

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