1) Vascular Reactivity to Alpha Adrenoceptor Agonists in Freely Moving SHR and WKY.

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There are reports of normal or increased responsiveness to alpha adrenoceptor agonist (alpha agonist) in vasculature of spontaneously hypertensive rats (SHR) when compared with normotensive Wistar Kyoto rats (WKY). However, most studies have done in isolated blood vessels in vitro and in anesthetized animals with pharmacological blockers or pithed animals in vivo. Therefore, despite the number of papers related to vascular reactivity, the contribution of increased vascular responsiveness to the development and/or maintenance of hypertension in SHR is controversial. The present study was designed to compare the vascular responsiveness to alpha agonist between freely moving SHR and WKY under condition of intact cardiovascular reflex.

Male SHR (15-week-old) and age-matched WKY were used. First, bipolar stainless-steel electrodes for electrical stimulation were chronically implanted into the mesencephalic reticular formation (MRF), and then 10 days after the surgery, an arterial and venous catheter were chronically placed in the abdominal aorta via the left iliac artery and inferior vena cava via the left femoral vein, respectively, as described previously (Kawasaki and Takasaki: J Pharmacol Exp Ther 236: 810, 1986). The blood pressure were measured through the arterial catheter under unanesthetized, unrestrained state. The heart rate (HR) was measured by a cardiograph triggered by arterial pulses. Both mean blood pressure (MBP) and HR were recorded on a polygraph and digitized by a minicomputer. Alpha agonists were dissolved in 0.9% sterile saline and injected intravenously (iv). The dose-response curve of maximum rise in mean blood pressure and of maximum decrease in HR were constructed by the method of stepwise iv administration of the agonist at 10 to 30-min intervals. MRF was stimulated electrically at 5 to 40 Hz for 5 sec (0.1 msec duration, 10 V) at 10 to 20-min intervals.

In both SHR and WKY, norepinephrine, a mixed alpha-1 and alpha-2 agonist, at doses of 0.03 to 1 µg/kg caused a dose-dependent rise in MBP with a reflex bradycardia. However, there is no significant difference in the dose-response curve for pressor response between SHR and WKY, while a decrease in HR was significantly smaller in SHR than in WKY. The pressor responses induced by the selective alpha-1 agonist, phenylephrine, at doses of 0.1 to 3 µg/kg and the selective alpha-2 agonist, α-methylnorepinephrine, at doses 0.03 to 3 µg/kg in SHR were similar to those in WKY. However, pressor responses induced by the highest dose (5 µg/kg) of both agonists were significantly greater than those in WKY. The bradycardiac responses to both agonists were significantly smaller in SHR than in WKY. Electrical stimulation of MRF at 5 to 40 Hz in both conscious SHR and WKY produced a frequency-dependent and a rapid rise in MBP, which were blocked by pretreatment with the ganglionic blocker, hexamethonium (25 mg/kg iv). Pressor responses to MRF stimulation in SHR were elicited by low frequencies (5 to 25 Hz) and were significantly greater than those in WKY.

From these results, the present study suggest that the vascular reactivity to alpha agonists in SHR with established hypertension is similar to that in WKY when observed under condition of intact cardiovascular reflex. However, greater responsiveness to brain stimulation in SHR suggests that the sympathetic outflow is enhanced in SHR and this mechanism may contribute to the maintenance of hypertension in SHR.