Pressor response to centrally administered clonidine in freely moving SHR and relations with body fluid volumes. Hiromu Kawasaki. Department of Pharmacology, Miyazaki Medical College, Miyazaki 889-16, Japan.

Clonidine is an antihypertensive drug. Its hypotensive effect has been believed to be due to the reduced peripheral sympathetic outflow as a result of stimulation of central $\alpha_2$-adrenoceptors (Kobinger: Rev Physiol Biochem Pharmacol 81: 40 1978). However, we have reported that clonidine produces a pressor response when administered intracerebroventricularly (i.c.v.), in freely moving, normotensive rats (Kawasaki and Takasaki: J Pharmacol Exp Ther 236: 810, 1986; Kawasaki et al.: Japan J Pharmacol 42: 405 1986). We further demonstrated that the pressor response to centrally administered clonidine is central in origin and mediated by central postsynaptic $\alpha_2$-adrenoceptors (Kawasaki and Takasaki: J Pharmacol Exp Ther 236: 810 1986) and that the clonidine-induced pressor response is inhibited by reduction of body fluid volumes (Kawasaki and Takasaki: Life Sci 40: 1929 1987). The present study was designed to investigate the pressor response to centrally administered clonidine in freely moving SHR by comparing with that in Wistar Kyoto normotensive rat (WKY).

Male SHR (15-16 weeks old) and age-matched WKY were subjected to implant chronically stainless steel guide cannulas into lateral cerebral ventricles and thereafter polyethylene catheters into the abdominal aorta via the femoral artery and the vena cava via femoral vein. Both blood pressure and heart rate were measured in an unanesthetized, unrestrained state while behavior was observed simultaneously, recorded on a polygraph and digitized by using a minicomputer at 1-min intervals. Central administration (i.c.v.) of clonidine was made in a volume of 5 $\mu$l. Central pretreatment (i.c.v.) with $\alpha$-adrenoceptor antagonists was performed in a volume of 10 $\mu$l 15 min before clonidine injection. Pentobarbital-Na and furosemide were administered 20 and 60 min before clonidine injection, respectively.

The $\alpha_2$-adrenoceptor agonist, clonidine (1 to 10 $\mu$g), when injected i.c.v., produced a dose-dependent and long-lasting pressor response concomitant with a decrease in HR. The depressor response to clonidine was observed in low doses (1 and 2.5 $\mu$g) but not high doses (5 and 10 $\mu$g). Both pressor and depressor response to clonidine were significantly greater in SHR than in WKY, while there was no significant difference in heart rate decreasing effect of clonidine between WKY and SHR. The clonidine-induced pressor response was abolished by central pretreatment with the $\alpha_2$-adrenoceptor antagonist, yohimbine (100 $\mu$g), but not with the $\alpha_1$-adrenoceptor antagonist, prazosin (10 $\mu$g). In both WKY and SHR anesthetized with pentobarbital-Na (50 mg/kg i.p.), i.c.v. injection of clonidine (5 and 10 $\mu$g) caused a slight pressor response and a marked depressor response concomitant with bradycardia. Furthermore, the pressor response to i.c.v. injected clonidine was inhibited by water deprivation for 24 hr or by furosemide treatment (5 mg/kg i.v.) and a depressor response was induced by clonidine. One day after surgery for catheters' implantation, SHR showed a significant decrease in water intake, and i.c.v. injection of clonidine produced a small pressor response and a marked depressor response. However, when the animal showed normal water intake on 7 days after the operation, i.c.v. injected clonidine produced a marked pressor response and a small depressor response.

These results suggest that the clonidine-induced pressor response, which results from stimulation of central $\alpha_2$-adrenoceptors, is enhanced in SHR and masks the central hypotensive response mediated by $\alpha_2$-adrenoceptors. It is also suggested that this pressor mechanism is sensitive to anesthesia and decrease in body fluid volumes.