Beta-adrenoceptor Subtypes in the Hypothalamic Paraventricular Nucleus of Spontaneously Hypertensive Rats. Hiromi Tsushima and Seigo Fujimoto. Department of Pharmacology, Nagoya City University Medical School, Nagoya 467.

Adrenergic neurons in the hypothalamic paraventricular nucleus (PVN) are suggested to play an important role to develop/maintain hypertension in spontaneously hypertensive rats (SHR) from the following findings: SHR with lesioned PVN or with intracerebro-ventricular injections of 6-hydroxydopamine delay developing hypertension, and there are differences between SHR and Wistar-Kyoto rats (WKY) in norepinephrine (NE) concentrations and activities of NE synthetic enzymes in the PVN or the hypothalamus. In addition, the PVN has cell bodies of vasopressin-containing neurons and regulates vasopressin release through beta-adrenergic mechanism. In this study, we investigated effects of beta-adrenoceptor agonists, microinjected into the PVN, on urine outflow rate and blood pressure; data in SHR were compared with those in WKY or Wistar rats (WR). METHODS: SHR (11-19 weeks old), WKY (10-20 weeks old) and WR (9-11 weeks old), starved for 18 hr, were used. After the rats were loaded with tap water (5 ml/100 g b.w.) and 45 min later, were anesthetized with the same volume of 12% ethanol, they were cannulated in the trachea, the urinary bladder, the jugular vein and artery. Drugs, except a vasopressin antagonist (d(CH₂)⁵-D-Tyr²(Et)Val⁴-Arg⁸-vasopressin), were microinjected into the PVN (5.6 mm anterior from lambda, 0.3 mm lateral to midline and 8.0 mm from the dura surface). During experiments, Locke's solution containing 3% ethanol was infused at 0.1 ml/min from the jugular vein cannula. Urinary drops flowing the bladder cannula were counted by a photoelectric drop counter. Blood pressure was measured directly from the jugular artery cannula. RESULTS AND DISCUSSION: Microinjections of isoproterenol (ISO, a non-selective beta-agonist), fenoterol (FEN, a beta-2 agonist) and T-1583 (a beta-1 agonist) into the PVN of SHR produced antidiuretic effects in a dose-dependent manner. The antidiuretic effects by ISO (20 nmol) began within 20 min, reached maximum at 30-40 min and ended by 90 min after the injection. The time-courses for the FEN- and T-1583-induced antidiureses were similar to that for the ISO-induced effect. The ED₅₀ values for ISO, FEN and T-1583 were 7, 3 and 80 nmol, respectively. Dobutamine (80 nmol, a beta-1 agonist) did not significantly influence urine outflow rate. In WKY and WR, these beta-agonists also reduced urine outflow rate, but they showed a tendency to be less potent than those in SHR. The antidiuretic response to FEN (5 nmol) in SHR and WKY were inhibited by pretreatment with atenolol (5 nmol, a beta-1 antagonist) or butoxamine (25 nmol, a beta-2 antagonist) applied into the PVN; the inhibitory effects were more potent in SHR than in WKY. The antidiuretic response to FEN in WR was inhibited by timolol (100 nmol, a non-selective beta-antagonist), but not by atenolol nor butoxamine. The vasopressin antagonist injected intravenously did not block the effects of FEN (5 nmol) in WKY. FEN (5 nmol) decreased blood pressure in SHR and WKY, but not in WR. It is suggested that 1) In the PVN, beta-2 adrenoceptor subtype predominantly regulates urine outflow rate. 2) This regulation does not involve increased vasopressin release. 3) Beta-adrenoceptor-mediating antidiureses in the PVN of SHR are more susceptible to the inhibition by beta-antagonists, compared with those of WKY and WR.