Hypotensive and bradycardic effects of centrally administered vasopressin in stroke-prone spontaneously hypertensive rats

Hypertension

American Heart Association®

Learn and Live℠

Hypotensive and bradycardic effects of centrally administered vasopressin in stroke-prone spontaneously hypertensive rats

Y Imai, K Abe, S Sasaki, N Minami, T Nobunaga, H Sekino and K Yoshinaga

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://hyper.ahajournals.org/content/10/3/346

Hypotensive and Bradycardic Effects of Centrally Administered Vasopressin in Stroke-Prone Spontaneously Hypertensive Rats

YUTAKA IMAI, KEISHI ABE, SHUICHI SASAKI, NAOYOSHI MINAMI, TOSHIMA NOBUNAGA, HIROSHI SEKINO, AND KAORU YOSHINAGA

The cardiovascular effects of centrally administered arginine vasopressin were studied in stroke-prone spontaneously hypertensive rats and Wistar-Kyoto rats. Arginine vasopressin was infused intracerebroventricularly into conscious rats at a rate of 2 pg/kg/min (4.6 μl/hr) for 21 hours, and blood pressure and heart rate were monitored. Arginine vasopressin caused transient hypertension and tachycardia in Wistar-Kyoto rats, whereas it induced delayed hypotension and bradycardia in stroke-prone spontaneously hypertensive rats. The effects on the latter lasted for 24 to 72 hours after cessation of the infusion. Intravenous administration of arginine vasopressin at a rate of 2 pg/kg/min did not cause any change in blood pressure and heart rate in these rats. These results suggest that arginine vasopressin acts centrally to depress cardiovascular activities, at least in stroke-prone spontaneously hypertensive rats. (Hypertension 10: 346–349, 1987)

RECENT studies have shown that there are extensive extrahypothalamic axonal projections of vasopressin neurons from the nuclei producing arginine vasopressin (AVP) precursor, the supraoptic nucleus and the paraventricular nucleus. The major projections appear to be to brainstem nuclei, including the nucleus tractus solitarii and dorsal vagal nucleus, and the intermediolateral nucleus of the spinal cord.[1, 2] Recently, the presence of AVP-containing cells has also been reported in nonhypothalamic nuclei in rats.[3, 4] All of these sites are known to be involved in central cardiovascular regulation, and this suggests that central vasopressin may act as a neuromodulator or a neurotransmitter (or both) involved in the central cardiovascular regulatory mechanisms. Furthermore, spontaneously hypertensive rats (SHR) and stroke-prone SHR (SHRSP) of the Okamoto-Aoki strain have been reported to have a lower concentration of AVP in brainstem and hypothalamic nuclei when compared with the normotensive parent strain, Wistar-Kyoto rats (WKY).[5-7]

Despite this circumstantial evidence, the putative role of central vasopressinergic mechanisms in cardiovascular regulation has not been fully elucidated. Recently, AVP has been shown to have specific and direct effects on the baroreceptor reflex function (see the recent review by Johnston[8]). Liard et al.[9] proposed that the locus of these effects is in the central nervous system. It has been observed that Brattleboro rats with hereditary hypothalamic diabetes insipidus have suppressed baroreceptor reflex function, and exogenous AVP administered systemically or centrally restored this function to the range in Long-Evans rats, the normal parent strain of Brattleboro rats.[10] Reduced baroreceptor reflex function has also been demonstrated in SHR.[11] Inhibition of central baroreceptor reflex pathways is generally considered to raise blood pressure.[12]

These links between blood pressure, baroreceptor reflex function, and AVP have prompted us to investigate whether centrally administered AVP depresses the blood pressure in SHR, especially in SHRSP.

Materials and Methods

We used male and female SHRSP (age, 19.5 ± 0.5 weeks; n = 7) and age-matched WKY (age, 20.2 ± 0.3 weeks; n = 7), obtained from the Institute for Experimental Animals, Tohoku University, Sendai, Japan. A cannula (PE-20 polyethylene tubing, 4.6 cm long with a volume of approximately 4.6 μl) was implanted into the left lateral ventricle with the rats under pentobarbital anesthesia. Coordinates for implantation with respect to the bregma were 1.0 mm posterior, 1.5 mm lateral, and 5 mm deep. The cannula was filled with artificial cerebrospinal fluid (ACSF) and fixed in place with stainless steel anchoring screws and orthopedic bone cement. Seven days after the cerebroventricular cannulation, the left femoral artery and vein were cannulated using polyethylene tubing (tapered PE-100 tubing for artery and PE-20 tubing for vein). The catheters were passed subcutaneously and brought out on the neck. The arterial catheter was connected to a hydraulic, swivel-tethering system, and each rat was placed in an individual plastic metabolic cage and housed under conditions of constant temperature (23°C) and humidity (60%), with a 12-hour light/dark cycle. To keep the arterial catheter patent, heparinized saline solution (100 U/ml) was continuously infused at a rate of 80 μl/hr.

The animals were fed a commercial diet and water ad libitum. Blood pressure was recorded from the femoral artery catheter using a P23Ib Statham pressure transducer (Oxford, CA, USA) and strain-gauge amplifier (Model 1257; NEC-San-ei, Tokyo, Japan). Heart rate was counted from phasic pressure wave by a cardiotachometer (Model 1321; NEC-San-ei). The analog signals of phasic pressure, mean arterial pressure, and heart rate were fed to an analog/digital converter (Mark 1; N.C.C., Tokyo, Japan). Digital signals of mean arterial pressure and heart rate from this converter were fed to a microcomputer (Model HP-9816; Hewlett-Packard, Fort Collins, CO, USA) every 4 seconds for 21 hours/day. The remaining 3 hours of the day was devoted to calculation and printout. At the end of each measurement period, the processed data were printed out. Mean values and the standard deviation averaged for each 10-minute, 1-hour, and 21-hour period were calculated for each parameter and plotted on time-trend charts and histograms.

To allow blood pressure and heart rate to stabilize, the experiment was started at least 72 hours after the operation. A time-control experiment was performed on the fourth postoperative day and consisted of an intracerebroventricular infusion of ACSF at a rate of 4.6 μl/hr. Twenty-four hours later, AVP (Protein Research Foundation, Osaka, Japan) was infused i.c.v. at a rate of 2 pg/kg/min (4.6 μl/hr) for 21 hours. AVP was dissolved into ACSF to the desired concentration. ACSF and AVP solutions were infused by means of a Princeton infusion pump (Model 575; Natick, MA, USA).

Following each infusion experiment, blood pressure and heart rate were monitored for 2 to 3 days to follow the recovery from the cardiovascular effects of the AVP infusion. The reproducibility of the time course of changes in blood pressure and heart rate in response to the i.c.v. infusion of ACSF (4.6 μl/hr) was examined in a separate experiment using eight WKY. The i.c.v. infusion of ACSF was performed on the fourth and sixth postoperative days. The effect of an intravenous infusion of AVP at a rate of 2 pg/kg/min was also examined in five SHRSP. The time course of cardiovascular changes was compared by two-way analysis of variance for repeated measures. Comparisons between values obtained at specific time points and the control value (zero hour in Figure 1) were made using Duncan's multiple range test.

Results

The basal mean arterial pressures in WKY and SHRSP were 118 ± 2 and 187 ± 12 mm Hg, respectively, and basal heart rates were 370 ± 6 and 356 ± 15 beats/min, respectively. The i.c.v. infusions of ACSF did not cause any cardiovascular changes. The time course of changes in mean arterial pressure ($F_{1,314} = 0.24$, $p > 0.8$) and heart rate ($F_{1,314} = 0.59$, $p > 0.4$) in response to i.c.v. ACSF infusion was sufficiently reproducible. The i.c.v. infusions of AVP induced a gradual decrease in mean arterial pressure in six of seven SHRSP (time control vs i.c.v. AVP infusion: $F_{1,239} = 96.9$, $p < 0.0001$). In the remaining rat, only an initial, transient increase in mean arterial pressure was observed. The i.c.v. infusions of AVP also induced a transient tachycardia followed by bradycardia in all SHRSP. The bradycardic effect reached its nadir 6 hours after the start of the infusion and was followed by gradual recovery to the initial level (time control vs i.c.v. AVP infusion: $F_{1,239} = 32.0$, $p < 0.0001$; Figure 1). In contrast to the response seen in SHRSP, i.c.v. infusions of AVP in WKY induced elevations of blood pressure and tachycardia that returned to the initial levels after 10 and 7 hours, respectively (see Figure 1). No significant hypotension (WKY vs SHRSP: $F_{1,259} = 194.2$, $p < 0.0001$) and bradycardia (WKY vs SHRSP: $F_{1,259} = 75.1$, $p < 0.0001$) were observed in WKY.

The hypotensive effect of i.c.v. AVP infusion in SHRSP persisted long after cessation of the infusion. In one rat it took 72 hours to recover the initial blood pressure level, while in the remaining rats the initial level was recovered within 48 hours. Figure 2 shows the time course of the changes in blood pressure during and after an i.c.v. infusion of AVP in a single experiment with SHRSP. The intravenous infusion of AVP at a rate of 2 pg/kg/min in SHRSP had no effect on blood pressure and heart rate (data not shown).

FIGURE 1. *Time course of changes in mean arterial pressure (MAP) and heart rate (HR) induced by i.c.v. infusions of artificial cerebrospinal fluid and of arginine vasopressin (AVP) at a rate of 2 pg/kg/min for 20 hours in WKY and SHRSP. Symbols and vertical bars represent the means and SEM. Asterisk indicates a significant difference (p<0.05) compared with control values (Hour 0), by Duncan's multiple range test.*
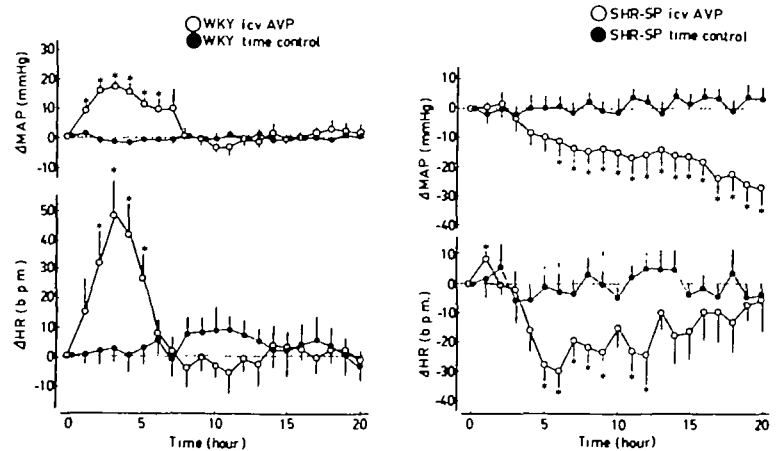
Discussion

The present study clearly demonstrates that protracted i.c.v. infusions of AVP in a low dose dramatically decrease blood pressure and heart rate in SHRSP and transiently increase these parameters in normal WKY. Previous studies found that centrally administered AVP caused hypertension and tachycardia in rats.[13-16] In these earlier studies, however, huge amounts of AVP were administered centrally for short periods to anesthetized or unanesthetized rats. In the present study we infused a small amount of AVP for a long period in a minimum infusion volume. Since rats weighing 300 g may have 400 μl of cerebrospinal fluid[17] and as the half-life of AVP in cerebrospinal fluid is only a few minutes,[18] the AVP concentration in cerebrospinal fluid of rats would attain a steady state concentration of 15 to 20 pg/ml according to the one-compartment-open model when AVP is administered i.c.v. at a rate of 2 pg/kg/min. This cerebrospinal fluid concentration of AVP might still be unphysiologically high, but it is certainly much closer to physiological levels as compared with those expected in previous short-term experiments.

Under such experimental conditions the previously reported hypertensive effect of centrally administered AVP was also observed in the present study in WKY. This effect may be mediated by midbrain or brainstem cardiovascular control mechanisms since microinjection of AVP to the nucleus tractus solitarii or locus ceruleus produces tachycardia and hypertension.[19, 20] However, vasopressinergic neuronal projections are not restricted to these regions; they are also found in other central cardiovascular centers, such as the anteroventral third ventricle of the hypothalamus, the dorsal vagal nucleus of the brainstem, and the intermediolateral nucleus of the spinal cord.[1, 2] These varied sites suggest that central vasopressinergic mechanisms have a dual function: to produce 1) cardiovascular stimulation and 2) cardiovascular depression. Central vasopressinergic neuronal mechanisms have been reported to attenuate the centrally mediated pressor responses to electrical stimulation of the mesencephalic reticular formation.[21] Furthermore, central injection of AVP causes bradycardia or hypotension, or both, in cats[22] and dogs.[23] More recently, Imai et al.[24] reported that centrally administered AVP caused hypotension
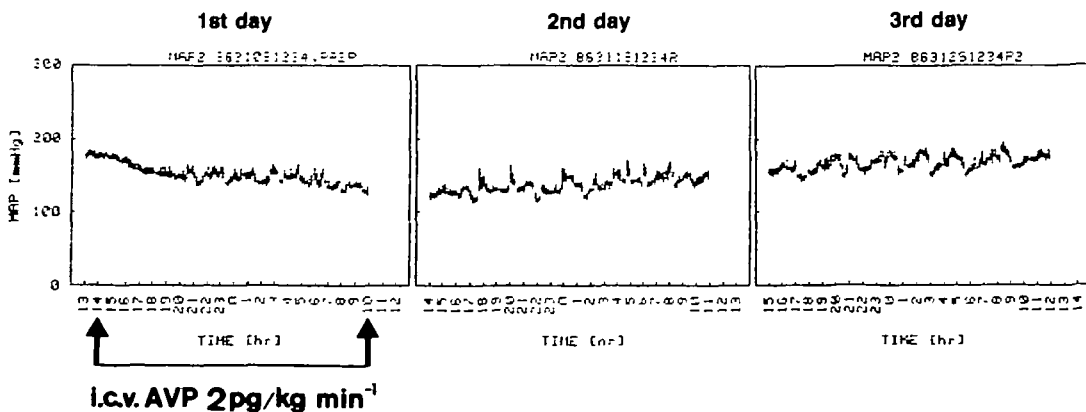

FIGURE 2. *Time course of changes in mean arterial pressure (MAP) in a single experiment during and after an i.c.v. arginine vasopressin (AVP) infusion at a rate of 2 pg/kg/min. Each vertical bar represents ± 1 SD of MAP averaged over 10 minutes. The numbers at the top of each panel are rat identification numbers.*

and bradycardia in rats with hereditary hypothalamic diabetes insipidus (Brattleboro) but not in normal Long-Evans rats. These lines of evidence are consistent with the hypothesis that decreased AVP levels in several brain loci of SHR[5-7] contribute to the induction and maintenance of high blood pressure in this strain of rat.

The precise reason why centrally administered AVP causes hypotension and bradycardia only in SHRSP is uncertain; however, the AVP-sensitive cardiovascular depressor center in SHRSP may be more sensitive to exogenous AVP than that in WKY. In normal WKY, endogenous AVP may occupy or desensitize the region where exogenous AVP induces cardiovascular depression in SHRSP; thus, additional AVP stimulation would cause no further decrease in blood pressure and heart rate. This hypothesis is supported by the evidence that the AVP content of the brainstem and hypothalamic nuclei in SHR and SHRSP is less than that in the normotensive strain.[5-7] One might even argue that AVP in certain central regions may protect against the development and maintenance of hypertension in rats.

The precise mechanism by which AVP modulates central cardiovascular centers has not been elucidated, although a number of studies have attempted to solve this question. For example, vasopressin has been shown to influence preganglionic sympathetic neurons to change phosphatidylinositol turnover and calcium kinetics in sympathetic ganglia and to modulate catecholamine turnover and metabolism in medullary brain nuclei (see the recent review by Johnston[8]). We observed that the hypotensive effect of i.c.v. AVP infusion in SHRSP persisted long after cessation of the infusion. Meisenberg and Simmons[18] reported that AVP in cerebrospinal fluid is easily destroyed by aminopeptidases and that its half-life in cerebrospinal fluid is only a few minutes. Two possibilities may explain the long-lasting hypotensive effect of AVP: 1) The activity of aminopeptidases may be attenuated in SHRSP. 2) Some metabolite of AVP may act centrally to cause hypotension. Some of the central effects of AVP, including those on behavior and memory, are very long lasting.[25] A protracted inhibitory effect of lysine vasopressin on the centrally mediated pressor response has also been reported.[21] The results of the present study are consistent with these earlier results, although we have no evidence to support either of the possible explanations.

References

1. Buijs RM, Swaab DF, Dogterom J, VanLeeuwen FW. Intra- and extrahypothalamic vasopressin and oxytocin pathways in the rat. Cell Tissue Res 1978;186:423–433
2. Sofroniew MV, Schrell U. Evidence for a direct projection from oxytocin and vasopressin neurons in the hypothalamic paraventricular nucleus to the medulla oblongata: immunohistochemical visualization of both the horseradish peroxidase transported and the peptide produced by the same neurons. Neurosci Lett 1981;22:211–217
3. Buijs RM, DeVreis GJ, VanLeeuwen FW, Swaab DF. Vasopressin and oxytocin: distribution and putative functions in the brain. Prog Brain Res 1983;60:115–122
4. Sofroniew MV. Vasopressin and oxytocin in the mammalian brain and spinal cord. Trends Neurosci 1983;6:467–472
5. Möhring J, Schoun J, Kintz J, McNeill R. Decreased vasopressin content in brain stem of rats with spontaneous hypertension. Naunyn Schmiedebergs Arch Pharmacol 1980;315:83–84
6. Rascher W, Lang RE, Unger T, Ganten D, Gross F. Vasopressin in brain of spontaneously hypertensive rats. Am J Physiol 1982;242:H496–H499
7. Morris M, Keller M, Sundberg DK. Changes in paraventricular vasopressin and oxytocin during the development of spontaneous hypertension. Hypertension 1983;5:476–481
8. Johnston CI. Vasopressin in circulatory control and hypertension. J Hypertens 1985;3:557–569
9. Liard JF, Deriaz O, Tschopp M, Schoun J. Cardiovascular effects of vasopressin infused into the vertebral circulation of conscious dogs. Clin Sci 1981;61:345–347
10. Imai Y, Nolan PL, Johnston CI. Restoration of suppressed baroreflex sensitivity in rats with hereditary diabetes insipidus (Brattleboro rats) by arginine-vasopressin and DDAVP. Circ Res 1983;53:140–149
11. Coote JH, Sato Y. Reflex regulation of sympathetic activity in the spontaneously hypertensive rat. Circ Res 1977;40:571–577
12. Ferrario CM, Gildenberg PL, McCubbin JW. Cardiovascular effects of angiotensin mediated by the central nervous system. Circ Res 1972;30:257–262
13. Feuerstein G, Zerbe RL, Faden AI. Central cardiovascular effects of vasotocin, oxytocin and vasopressin in conscious rats. J Pharmacol Exp Ther 1984;228:348–353
14. Imai Y, Nolan PL, Johnston CI. Role of vasopressin in blood pressure regulation through its modulatory effect on baroreceptor reflex. In: Sambhi MP, ed. Fundamental fault in hypertension. Boston: Martinus Nijhoff, 1984:251–260
15. Pittman QJ, Lawrence D, McLean L. Central effects of arginine vasopressin on blood pressure in rats. Endocrinology 1982;110:1058–1060
16. Zerbe RL, Kirtland S, Faden AI, Feuerstein G. Central cardiovascular effects of mammalian neurohypophyseal peptides in conscious rats. Peptide 1983;4:627–630
17. Meek JL, Neff NH. Is cerebrospinal fluid the major avenue for the removal of 5-hydroxyindoleacetic acid from the brain? Neuropharmacology 1973;12:497–499
18. Meisenberg G, Simmons WH. Factors involved in the inactivation of vasopressin after intracerebroventricular injection in mice. Life Sci 1984;34:1231–1240
19. Mastuguchi H, Schmid PG. Blood pressure and heart rate responses to microinjection of vasopressin into the nucleus tractus solitarius region of the rat. Neuropharmacology 1982;21:687–693
20. Berecek KH, Olpe HR, Jones RSG, Hofbauer KG. Microinjection of vasopressin into the locus coeruleus of conscious rats. Am J Physiol 1984;247:H675–H681
21. Versteeg CAM, Bohus B, DeJong W. Attenuation by arginine- and desglycinamide-lysine-vasopressin of a centrally evoked pressor response. J Auton Nerv Syst 1982;6:253–262
22. Nashold BS, Mannarino E, Wunderlich M. Pressor-depressor blood pressure responses in the cat after intraventricular injection of drugs. Nature 1962;193:1297–1298
23. Varma S, Jaju BP, Bhargava KP. Mechanism of vasopressin-induced bradycardia in dogs. Circ Res 1969;24:787–792
24. Imai Y, Sasaki S, Abe K, Minami N, Sekino H, Yoshinaga K. Centrally mediated hypotensive and blood pressure stabilizing effect of vasopressin in Brattleboro rat. J Hypertens 1987 (in press)
25. DeWied D, Versteeg DHG. Neurohypophyseal principles and memory. Fed Proc 1979;38:2348–2354