

# **Role of Vasopressin in Cardiovascular and Neurohormonal Responses to Intracerebroventricular Hypertonic NaCl**

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## **SUMMARY**

To determine the significance of vasopressin in cardiovascular and neurohormonal responses caused by centrally administered hypertonic NaCl, we examined the effects of a vasopressin antagonist on blood pressure, heart rate, plasma levels of catecholamines, cortisol and renin activity in anesthetized dogs.

Intracerebroventricular (ICV) injections of 0.2 ml of 1.5 M NaCl increased mean arterial blood pressure ( $+29.7 \pm 3.0$  mmHg, mean  $\pm$  SE), heart rate ( $+27.9 \pm 7.0$  beats/min), plasma concentrations of vasopressin ( $+48.9 \pm 8.2$  pg/ml), norepinephrine ( $+40.0 \pm 6.2$  pg/ml), epinephrine ( $+231.4 \pm 21.4$  pg/ml) and cortisol ( $+5.3 \pm 1.1$   $\mu$ g/dl) and decreased plasma renin activity ( $-2.0 \pm 0.4$  ng/ml/hr). An intravenous vasopressin antagonist, d(CH<sub>2</sub>)<sub>5</sub>Tyr(Me)AVP, at a dose of 10  $\mu$ g/kg, attenuated the pressor response and augmented the heart rate response to ICV 1.5 M NaCl. The vasopressin antagonist also augmented the change in plasma norepinephrine and significantly attenuated the responses of cortisol and renin. Baseline levels of these variables were not altered by the vasopressin antagonist except for an increase in renin activity. Two injections of hypertonic NaCl without any pretreatment produced similar cardiovascular and hormonal responses.

These results suggest that vasopressin contributes not only to an increase in blood pressure, but also to changes in the sympathetic nervous system, the hypothalamo-adrenocortical axis and the peripheral renin-angiotensin system in response to a central sodium stimulus.

## **Additional Indexing Words:**

Blood pressure    Central nervous system    Catecholamine    Renin  
Cortisol

**T**HE sodium concentration in the central nervous system may play an important role in cardiovascular and body fluid regulation. Hypertonic sodium chloride (NaCl) administered into the brain ventricle produces blood

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pressure elevation, thirst and natriuresis associated with neurohormonal changes such as activation of the sympathetic nervous system with inhibition of renal nerve activity, release of vasopressin and cortisol, and suppression of plasma renin activity.<sup>1)-5)</sup> In contrast, a decrease in sodium concentration in the cerebrospinal fluid (CSF) results in antinatriuresis, suppression of vasopressin and an increase in renin release.<sup>3),6)</sup>

We observed that released vasopressin participated in the pressor response to intracerebroventricular (ICV) hypertonic NaCl in the dog<sup>5)</sup> although the sympathetic nervous system appears to play a major role in this response.<sup>4)</sup> It is possible that vasopressin may also contribute to other neurohormonal changes induced by ICV hypertonic NaCl since it is known that vasopressin interacts with the baroreceptor reflex to inhibit sympathetic activity,<sup>7)</sup> releases adrenocorticotrophic hormone,<sup>8)</sup> and suppresses renin release.<sup>9)</sup> To clarify this possibility, we examined the effects of a vasopressin antagonist on the cardiovascular and neurohormonal responses to ICV hypertonic NaCl in the dog.

## METHODS

### *Animal preparation:*

Twelve male mongrel dogs weighing between 17 and 23 kg were anesthetized with intramuscular morphine sulphate (2 mg/kg) and intravenous (IV) sodium pentobarbital (15 mg/kg). The animals were mechanically ventilated after tracheal intubation. A catheter was inserted into the femoral artery for blood pressure recording and blood sampling. Another catheter was inserted into the femoral vein for IV administration. A 20-gauge needle was placed into the left lateral ventricle stereotactically and was fixed to the skull with dental cement as described previously.<sup>10)</sup> Proper placement of the cannula was ascertained by obtaining cerebrospinal fluid.

### *Experimental protocol:*

Hypertonic NaCl (0.2 ml of 1.5 M NaCl) was injected into the lateral ventricle over 1 min. We observed previously that this dose of hypertonic NaCl produced significant pressor and tachycardic responses with neurohormonal changes, while ICV administration of the same amount of physiological saline had no effects in anesthetized dogs.<sup>4)</sup> In 8 dogs, a vasopressin antagonist, d(CH<sub>2</sub>)<sub>5</sub>Tyr(Me)AVP (Calbiochem., USA) at a dose of 10 µg/kg, was given intravenously 1 hour after the first ICV 1.5 M NaCl injection. Fifteen minutes later, the second ICV 1.5 M NaCl injection was carried out. The vasopressin antagonist (VPA) abolished the pressor response to IV vasopressin

at a dose of 300  $\mu\text{g/kg}$  for more than 2 hours in our preliminary experiment. In the other 4 dogs, repeated administration of ICV hypertonic NaCl was performed with a 75 min interval to test the reproducibility of this stimulus.

Blood pressure and heart rate were monitored continuously throughout the experimental period in all animals. Arterial blood was taken before and 10 min after ICV 1.5 M NaCl to measure plasma concentrations of vasopressin and catecholamines, and before and 20 min after for determination of cortisol and renin. These sampling times were in accord with the peak response of each hormone induced by ICV hypertonic NaCl in our previous study.<sup>4)</sup> Blood samples were also obtained before and 15 min after administration of VPA in the 8 dogs.

#### *Measurements and data analysis:*

Arterial blood pressure was recorded with a strain gauge pressure transducer (Statham P23db, Gould Inc., USA) and heart rate was computed by feeding the electrocardiogram into a bio-tachometer (Biotach Amplifier, Gould Inc.). Plasma concentrations of free norepinephrine and epinephrine were determined by radioenzymatic assay. Levels of vasopressin, cortisol and renin activity were measured by radioimmunoassay.

All variables are expressed as mean  $\pm$  SE. Statistical analysis was performed by analysis of variance and by Student's t-test. A p value of less than 0.05 was considered statistically significant.

## RESULTS

In 8 dogs, 1.5 M NaCl was given before and after IV VPA. Table I shows cardiovascular and neurohormonal responses to the first ICV injection of 1.5 M NaCl. Arterial blood pressure and heart rate gradually increased

Table I. Cardiovascular and Neurohormonal Responses to Intracerebroventricular 1.5 M NaCl in 8 Dogs

	Before ICV	After ICV	Changes
Mean blood pressure (mmHg)	108.8 $\pm$ 4.1	138.5 $\pm$ 4.1	29.7 $\pm$ 2.5***
Heart rate (beats/min)	58.1 $\pm$ 3.4	86.0 $\pm$ 7.2	27.9 $\pm$ 7.0**
Plasma vasopressin (pg/ml)	9.0 $\pm$ 1.4	57.9 $\pm$ 8.6	48.9 $\pm$ 8.2**
Plasma norepinephrine (pg/ml)	56.0 $\pm$ 12.9	96.0 $\pm$ 15.4	40.0 $\pm$ 6.2**
Plasma epinephrine (pg/ml)	23.4 $\pm$ 5.5	254.8 $\pm$ 23.8	231.4 $\pm$ 21.4***
Plasma cortisol ( $\mu\text{g/dl}$ )	3.5 $\pm$ 0.6	8.8 $\pm$ 1.3	5.3 $\pm$ 1.1**
Plasma renin activity (ng/ml/hr)	6.5 $\pm$ 1.4	4.5 $\pm$ 1.3	-2.0 $\pm$ 0.4**

\*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

Table II. Effects of Intravenous d(CH<sub>2</sub>)<sub>5</sub>Tyr(Me)AVP (VPA) on Cardiovascular and Neurohormonal Variables in 8 Dogs

	Before VPA	Changes after VPA
Mean blood pressure (mmHg)	109.3± 4.2	-1.2±0.6
Heart rate (beats/min)	60.0± 2.8	1.6±0.8
Plasma norepinephrine (pg/ml)	58.8±14.0	2.6±5.1
Plasma epinephrine (pg/ml)	32.4± 7.9	-3.2±6.4
Plasma cortisol (μg/dl)	2.9± 0.4	-0.1±0.1
Plasma renin activity (ng/ml/hr)	6.6± 1.5	1.5±0.5*

\* p&lt;0.05.

after ICV administration and peaked at approximately 10 min, then returned to baseline levels within 60 min. These changes were associated with significant increases in the plasma levels of vasopressin, norepinephrine, epinephrine and cortisol, and a decrease in plasma renin activity.

Intravenous VPA did not affect the baseline levels of these cardiovascular and neurohormonal variables except for a small increase in plasma renin activity (Table II). Figure 1 shows the cardiovascular and neurohormonal changes induced by ICV 1.5 M NaCl before and after administration of VPA. Compared with the first ICV NaCl, the second ICV 1.5 M NaCl after VPA produced a smaller increase in mean blood pressure (reduced by  $7.3\pm2.1$  mmHg,  $p<0.01$ ) and a greater heart rate response (augmented by  $15.3\pm4.6$  beats/min,  $p<0.01$ ). The second ICV NaCl also resulted in a larger increase in plasma norepinephrine ( $26.4\pm8.5$  pg/ml,  $p<0.05$ ), a comparable increase in epinephrine ( $7.4\pm17.7$  pg/ml), and smaller responses in plasma cortisol ( $1.5\pm0.5$  μg/dl,  $p<0.05$ ) and renin activity ( $1.0\pm0.4$  ng/ml/hr,  $p<0.05$ ).

In 4 dogs, ICV 1.5 M NaCl was given twice without any treatment. The changes in mean blood pressure and heart rate in response to the second ICV NaCl were not significantly different from those to the first administration (Fig. 2). The two ICV injections also had comparable effects on plasma levels of norepinephrine, epinephrine, cortisol and renin activity.

## DISCUSSION

In this study, intracerebroventricular administration of hypertonic NaCl increased blood pressure, heart rate, plasma levels of vasopressin, norepinephrine, epinephrine and cortisol, and decreased plasma renin activity, as observed previously.<sup>1)-5)</sup> The pressor response was inhibited by a vasopressin antagonist which blocked the vasoconstrictive action of vasopressin.<sup>11)</sup> This

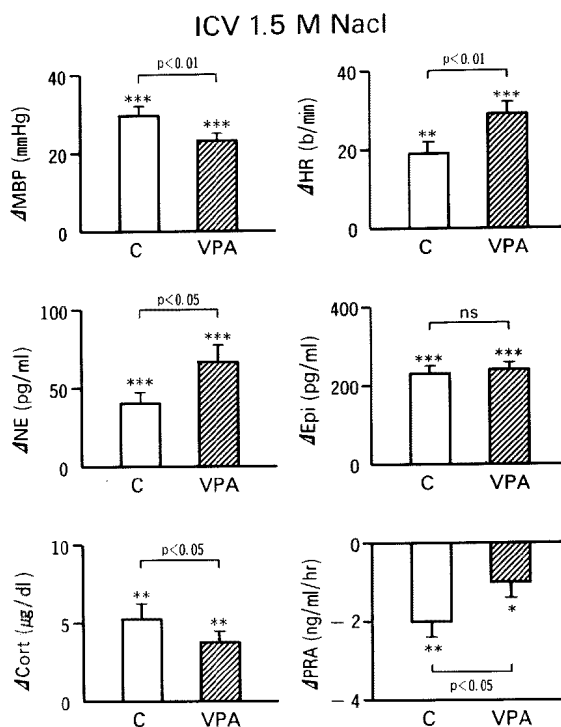


Fig. 1. Cardiovascular and neurohormonal responses to intracerebroventricular (ICV) 1.5 M NaCl before (C) and after treatment with intravenous vasopressin antagonist (VPA) in 8 dogs. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  compared with the baseline levels.

result confirms the contribution of vasopressin to the central pressor action of sodium,<sup>5)</sup> though we have demonstrated that the sympathetic nervous system plays a dominant role in the pressor response in the dog.<sup>4)</sup>

Our study indicates that vasopressin plays a role in the changes of other neurohormonal factors induced by ICV hypertonic NaCl. After treatment with the vasopressin antagonist, ICV hypertonic NaCl produced greater increases in heart rate and plasma norepinephrine than ICV NaCl alone. We previously observed that ICV hypertonic NaCl suppressed the renal sympathetic nerve activity in anesthetized dogs, but it activated the renal nerve activity after administration of the vasopressin antagonist<sup>5)</sup> or baroreceptor denervation.<sup>10)</sup> Therefore, the released vasopressin appears to inhibit activation of the sympathetic nervous system by ICV hypertonic NaCl. These observations are in accord with previous studies which have shown that vasopressin interacts with the baroreceptor reflex to suppress the sympathetic nervous system.<sup>7),12)</sup>

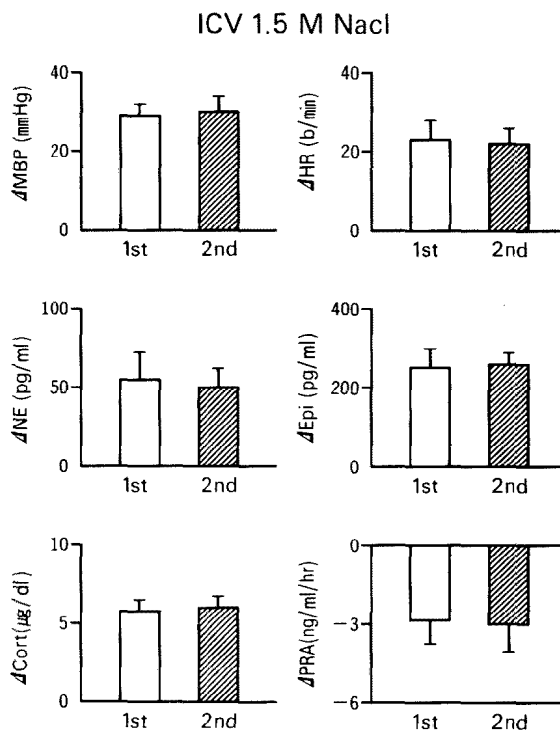


Fig. 2. Cardiovascular and neurohormonal responses to repeated administration of ICV 1.5 M NaCl in 4 dogs.

Plasma cortisol levels increased in response to ICV hypertonic NaCl, indicating stimulation of the hypothalamo-adrenocortical axis. Pretreatment with the vasopressin antagonist significantly attenuated but did not abolish the cortisol response. It is known that vasopressin stimulates release of adrenocorticotrophic hormone and potentiates the activity of corticotropin releasing factor.<sup>8),13)</sup> Aizawa et al have shown that this action of vasopressin is related to its pressor activity<sup>8)</sup> although involvement of another subtype of vasopressin receptor has been proposed by Baertschi and Friedli.<sup>14)</sup> Our results suggest that vasopressin mediates at least partly the activation of the hypothalamo-adrenocortical axis induced by the central sodium stimulus. The blunted cortisol response after a vasopressin antagonist could not be attributed to the smaller increase in blood pressure since an increase in blood pressure may act to suppress the hypothalamo-adrenocortical system via the baroreceptor reflex.<sup>15)</sup>

Vasopressin inhibits renin release.<sup>9),16)</sup> This action of vasopressin also may be related to its vasoconstrictive property since Johnson et al observed that DDAVP, a nonpressor analog of vasopressin with a potent antidiuretic

effect, failed to decrease plasma renin activity in the dog.<sup>16)</sup> In this study, the vasopressin antagonist attenuated the decrease in plasma renin activity induced by ICV hypertonic NaCl, suggesting that vasopressin may have a role in centrally mediated renin suppression by NaCl. The vasopressin antagonist also increased baseline renin levels in this study, supporting the influence of vasopressin in renin release in some physiological conditions. It is possible that a decrease in renal nerve activity induced by ICV hypertonic NaCl<sup>4)</sup> participates in the suppression of plasma renin activity. Since we observed that the vasopressin antagonist reversed the renal nerve response to ICV hypertonic NaCl,<sup>5)</sup> the effect of the vasopressin antagonist on renin response might be mediated by the renal nerve. Indeed, Gregory and Reid reported that the action of vasopressin on renin release depended on intact renal nerves in the dog.<sup>17)</sup>

It has been suggested that vasopressin contributes to natriuresis during ICV hypertonic NaCl<sup>3)</sup> although the sympathetic nervous system<sup>2)</sup> and hemodynamic changes<sup>2),18)</sup> may be involved in this phenomenon. The mechanisms of the vasopressin-mediated natriuresis are not understood completely. However, this study and previous observations suggest that vasopressin may contribute to the CNS-induced natriuresis through its pressor action and the inhibitory effects on the sympathetic nervous system and the renin-angiotensin system. The central nervous system responds to sodium loading with neurohormonal changes, including vasopressin release. These changes stimulate renal sodium excretion, resulting in a decrease in sodium concentration in plasma and extracellular fluid in the brain. It seems to be a well organized feedback system to maintain body fluid homeostasis, and vasopressin may play an important role in the central action of sodium.

## REFERENCES

1. Andersson B, Eriksson L, Fernández O, Kolmodin CG, Oltner R: Centrally mediated effects of sodium and angiotensin II on arterial blood pressure and fluid balance. *Acta Physiol Scand* **85**: 398, 1972
2. Chiu PJS, Sawyer WH: Third ventricular injection of hypertonic NaCl and natriuresis in cats. *Am J Physiol* **226**: 463, 1974
3. Mouw DR, Vander AJ, Landis C, Kutshinski S, Mathias N, Zimmerman D: Dose-response relation of CSF sodium and renal sodium excretion, and its absence in homozygous Brattleboro rats. *Neuroendocrinology* **30**: 206, 1980
4. Kawano Y, Ferrario CM: Neurohormonal characteristics of the cardiovascular response due to intraventricular hypertonic sodium chloride. *Am J Physiol* **247**: H422, 1984
5. Ferrario CM, Mikami H, Michelini LC, Kawano Y, Brosnihan KB: Interaction of vasopressin with central neurogenic mechanisms of blood pressure regulation. *in* Vasopressin, ed by Schrier RW, Raven Press, New York, p 47, 1985
6. Mouw DR, Vander AJ: Evidence for brain Na receptors controlling renal Na excretion and

- plasma renin activity. *Am J Physiol* **219**: 822, 1970
7. Cowley AW Jr, Monas E, Guyton AE: Interaction of vasopressin and the baroreceptor reflex system in the regulation of arterial blood pressure in the dog. *Circ Res* **34**: 505, 1974
  8. Aizawa T, Yasuda N, Greer MA, Sawyer WH: In vitro adrenocorticotropin-releasing activity of neurohypophyseal hormones and their analogs. *Endocrinology* **110**: 98, 1982
  9. Bunag RD, Page IH, McCubbin JW: Inhibition of renin release by vasopressin and angiotensin. *Cardiovasc Res* **1**: 67, 1967
  10. Takishita S, Ferrario CM: Lack of interaction between a hypertonic NaCl stimulus and the brain renin-angiotensin system. *Am J Physiol* **244**: H471, 1983
  11. Kruzynski M, Lammek B, Manning M: [1-( $\beta$ -Mercapto- $\beta$ , $\beta$ -cyclopentamethylene-propionic acid), 2-( $\alpha$ -methyl)tyrosine] arginine vasopressin and [1-( $\beta$ -Mercapto- $\beta$ , $\beta$ -cyclopentamethylene-propionic acid)] arginine vasopressin, two highly potent antagonists of the vasopressor response to arginine vasopressin. *J Med Chem* **23**: 364, 1980
  12. Undesser KP, Hassler EM, Haywood JR, Johnson AK, Bishop VS: Interactions of vasopressin with the area postrema in arterial baroreflex function in conscious rabbits. *Circ Res* **56**: 410, 1985
  13. McCann SM, Fruit A: Effect of synthetic vasopressin on release of adrenocorticotropin in rats with hypothalamic lesions. *Proc Soc Exp Biol Med* **96**: 566, 1957
  14. Baertschi AJ, Friedli M: A novel type of vasopressin receptor on anterior pituitary corticotrophs? *Endocrinology* **116**: 499, 1985
  15. Brooks VL, Reid IA: Interaction between angiotensin II and the baroreceptor reflex in the control of adrenocorticotrophic hormone secretion and heart rate in conscious dogs. *Circ Res* **58**: 816, 1986
  16. Johnson MD, Kinter LB, Beaukes R: Effects of AVP and DDAVP on plasma renin activity and electrolyte excretion in conscious dogs. *Am J Physiol* **236**: F66, 1979
  17. Gregory LC, Reid IA: Effect of renal denervation on the suppression of renin secretion by vasopressin in conscious dogs. *Am J Physiol* **247**: F881, 1984
  18. Bealer SL: Hemodynamic mechanisms in CNS-induced natriuresis in the conscious rat. *Am J Physiol* **244**: F376, 1983