Baroreceptor Influences on Oxytocin and Vasopressin Secretion

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The objective of these studies was to investigate the role of arterial baroreceptors in the control of neurohypophyseal secretion. The effect of sinoaortic denervation on basal and osmotic-induced release of oxytocin and vasopressin and on blood pressure was determined. Hypertonic or isotonic saline was infused intravenously into sham-operated or denervated rats 3 days after surgery. Plasma oxytocin and vasopressin were measured at 5 and 15 minutes after the infusion. The control levels of oxytocin were increased in the denervated rats, but vasopressin levels were not significantly altered. The vasopressin and oxytocin responses to hypertonic saline were greater after baroreceptor denervation. Plasma oxytocin was increased from 4.7±0.9 to 72.2±8.7 pg/ml in the denervated rats and from 1.8±0.3 to 39.9±6.7 pg/ml in the sham-operated control group at 5 minutes after the infusion (p<0.01). The plasma vasopressin response to hypertonic saline was 7.1±0.6 pg/ml in the sham-operated versus 11.1±1.6 pg/ml in the denervated rats (p<0.05). There was no difference between sham-operated and denervated rats in the effect of hypertonic saline on plasma sodium and hematocrit. Mean arterial blood pressure was increased after sinoaortic denervation (116.3±4.2 mm Hg in the sham-operated vs. 138.2±8.3 mm Hg in the denervated rats, p<0.05); however, there was no difference in the pressor response to hypertonic saline. These results show that the baroreceptor system influences the secretion of both oxytocin and vasopressin, with effects on basal secretion as well as the response to an osmotic stimulus. These changes may be important in the regulation of cardiovascular and fluid balance under conditions of baroreceptor deficiency. (Hypertension 1989;13:110-114)

Information on the status of the cardiovascular system is conveyed to the central nervous system by afferent fibers in the glossopharyngeal and vagus nerves. These primary afferents terminate mainly in the nucleus tractus solitarii with secondary pathways projecting to higher brain structures. Although these pathways are not completely known, brainstem noradrenergic centers are known to receive visceral afferent information and to send projections to the paraventricular and the supraoptic hypothalamic neurohypophyseal nuclei.

Information on the role of baroreceptor input is provided by studies of the effects caused by surgical interruption of the arterial baroreceptor nerves.

Results show that sinoaortic denervation (SAD) has widespread effects on both the cardiovascular and endocrine systems; there are increases in blood pressure, sympathetic nerve activity, and vasopressin secretion, while plasma prolactin and atrial natriuretic peptide concentrations are reduced. Results show that sinoaortic denervation (SAD) has widespread effects on both the cardiovascular and endocrine systems; there are increases in blood pressure, sympathetic nerve activity, and vasopressin secretion, while plasma prolactin and atrial natriuretic peptide concentrations are reduced. Results show that sinoaortic denervation (SAD) has widespread effects on both the cardiovascular and endocrine systems; there are increases in blood pressure, sympathetic nerve activity, and vasopressin secretion, while plasma prolactin and atrial natriuretic peptide concentrations are reduced.

The objective of the present study was to further explore the nature of baroreceptor influences on the control of the neurohypophyseal axis. The effect of SAD on the response of oxytocin and vasopressin to a peripheral osmotic challenge was determined.

Materials and Methods

Male Wistar rats (250–300 g; Charles River Inc., Boston, Massachusetts) were housed singly under conditions of controlled light (12-hour light/dark cycle) and temperature. They were fed normal rat chow (Purina Inc., St. Louis, Missouri) and tap water ad libitum. Either SAD or sham surgery was performed as previously described according to the method of Krieger. After the surgery, the SAD and sham-operated rats were divided into matched pairs. The food and water available to the sham-operated rats was matched to the intake of the SAD rats. This was done to eliminate the possibility of intake-induced...
changes in the responses. Jugular, and in some cases aortic, catheters (PE 50) were inserted while the rats were under ether anesthesia 24 hours before the experiment.

The rats were tested at 3 days after surgery. The experimental protocol was as follows: The rats were brought into the laboratory in their home cage (2 hours before the experiment). Hypertonic saline or isotonic saline (180 μl/100 g body wt of 18% NaCl or 0.9% NaCl) was infused over a 20–40-second period into conscious animals. The rats were decapitated either 5 or 15 minutes later and blood was collected in chilled tubes containing EDTA (final concentration 2 mg/ml). A small sample was collected in ammonium heparin for the measurement of plasma sodium. Hematocrit was also measured. The blood was centrifuged at 4°C and the plasma stored at −70°C. The neurohypophysis was removed and stored frozen at −70°C.

In a separate experiment, the effect of the hypertonic stimulus on blood pressure was measured via an aortic catheter. In this case, the catheter was connected to a Micron pressure transducer (Micron Inc., Los Angeles, California) and mean arterial blood pressure was recorded with a two-channel Gould Recorder (Gould Inc., Cleveland, Ohio). The lability of mean arterial pressure over time was an indication of successful denervation. Blood pressure was recorded continuously for 30 minutes before and 60 minutes after the infusion. Cardiovascular and endocrine measurements were not obtained from the same rats because of the possibility that stress might influence the hormonal response.

Plasma and tissue levels of oxytocin and vasopressin were measured by specific and sensitive radioimmunoassays. These assays were performed according to previously published methods. Iodine-125-labeled peptides were purchased from New England Nuclear (Du Pont Inc., Wilmington, Delaware) and the synthetic standards from Bachem (Bachem Inc., Torrance, California). The plasma samples (1 ml) were extracted before radioimmunoassay with the acetone/petroleum ether method. The neurohypophysis was homogenized in 0.1N HCl and the extract diluted before radioimmunoassay. The tissue and plasma extracts were dried with a Speed Vac Concentrator (Savant Instrs., Inc., Farmingdale, New York). Statistical analysis was by two-way analysis of variance (ANOVA) and a post hoc test (Duncan’s multiple range test). The plasma oxytocin data was subjected to log transformation before analysis. A p value of <0.05 was considered significant.

**Results**

An increase in the control levels of plasma oxytocin was produced by SAD while plasma vasopressin was not significantly changed (Figures 1 and 2). Basal levels are those measured in samples from sham-operated and SAD rats infused with isotonic saline. The increase in oxytocin was noted only in the samples collected at 5 minutes after infusion (1.8±0.3 pg/ml in sham-operated vs. 4.7±0.9 pg/ml in SAD rats, p<0.01).

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Bar graph showing changes in plasma oxytocin in response to intravenous isotonic (IS) or hypertonic saline (HS). A two-way analysis of variance on log-transformed data showed a significant effect of type (sham-operated vs. sinoaortic denervation [SAD] rats) and treatment (IS vs. HS); p<0.001, F=27.7 and p<0.001, F=513, respectively. n, 8–13 rats/group. **p<0.01 for sham-operated vs. SAD rats and ††p<0.01 for IS vs. HS treatment (Duncan’s multiple range test). Values are mean±SEM.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Bar graph showing changes in plasma vasopressin in response to intravenous isotonic (IS) or hypertonic saline (HS). A two-way analysis of variance showed a significant effect of type (sham-operated vs. sinoaortic denervation [SAD] rats) and treatment (IS vs. HS); p<0.001, F=17.9 and p<0.001, F=51.1, respectively. n, 8–14 rats/group. *p<0.05 and ++p<0.01 for sham-operated vs. SAD rats. *p<0.05 and ††p<0.01 for IS vs. HS treatment (Duncan’s multiple range test). Values are mean±SEM.
The hormonal responses to an osmotic challenge were also altered by SAD. The oxytocin response to intravenous hypertonic saline was markedly increased in the denervated rat (Figure 1; two-way ANOVA, p<0.001, F=27.7). The greatest change was noted at 5 minutes with levels of 72.2±8.7 pg/ml in the SAD compared with 39.9±6.7 pg/ml in the sham-operated rats. There was also an increase in the vasopressin response to hypertonic saline after denervation (Figure 2; two-way ANOVA, p<0.001, F=17.9). Plasma vasopressin was 7.1±0.6 pg/ml in the sham-operated group compared with 11.1±1.6 pg/ml in the SAD group at 5 minutes after the hypertonic saline infusion. However, the stimulation of plasma vasopressin was less than that observed for oxytocin. There was a 15-20-fold increase in oxytocin compared with a twofold change in vasopressin.

Plasma sodium was increased after hypertonic saline as expected; however, there was no statistical difference between the two groups (Table 1). Hematocrit was reduced by the osmotic stimulus; again, there was no significant difference between the sham-operated and SAD rats (Table 1). There was no difference in neurohypophyseal oxytocin and vasopressin at the time points measured (Table 1).

Hypertonic saline also produced an increase in blood pressure (Table 2). Basal mean arterial pressure was elevated in the SAD rats, 138.2±8.3 mm Hg versus 116.3±4.2 mm Hg in the sham-operated rats (p<0.05). The peak pressor response occurred at approximately 5 minutes after infusion. There was no difference in the responses between the sham-operated and SAD groups (percentage change from control).

### Discussion

These results confirm that the arterial baroreceptor system has potent influences on the neurohypophyseal axis under control and stimulated conditions. Denervation of the baroreceptor nerves caused a modest increase in the basal levels of oxytocin and a marked stimulation of osmotic-induced release of both oxytocin and vasopressin.

Previous results from this laboratory showed that SAD was associated with an increase in the circulating levels of vasopressin.4 This change was most prevalent in the early postoperative periods when blood pressure was highest. Thus, baroreceptor input to the hypothalamus was thought to be inhibitory, with removal resulting in a stimulation of secretion. However, in the present study, vasopressin levels were not significantly elevated at 3 days after denervation. The reason for the difference in results is not known. SAD did have an effect on oxytocin secretion; there was a modest rise in plasma oxytocin in the denervated rat.

In contrast to the rather small changes in basal hormone secretion elicited by denervation, there was a pronounced increase in the response to intravenous hypertonic saline. It is not known whether baroreceptor denervation specifically alters the osmoreceptors or acts through other mechanisms. It would be valuable to test the effect of other stimuli (i.e., hemorrhage or angiotensin) known to activate the neurohypophyseal system to determine whether there was a generalized change in sensitivity after denervation. In other studies in the dog and rabbit, SAD did not influence the vasopressin response to hemorrhage.10,11
These results confirm previous studies, which show that osmotic changes cause a greater release of oxytocin and oxytocin-neurophysin rather than vasopressin. The physiological significance of this finding is not clear. However, oxytocin does influence salt and water excretion and has effects on blood pressure and cardiac output. This neurotic also caused an activation of cells in the dorsal vagal nucleus of the brainstem.

One must also consider the interactions between osmotic, volume, and pressor stimuli. Previous results have shown that osmotic and volume factors are involved in the regulation of vasopressin and oxytocin secretion. For example, volume depletion, which lowers blood pressure, potentiated the response to an osmotic stimulus. The results of the present study are complicated by the fact that the osmotic challenge also has cardiovascular effects. Thus, feedback from the increase in blood pressure could modulate the hormonal responses. In the denervated animal this afferent signal would be absent, resulting in an increased hormonal response. However, this does not explain the elevation of basal secretion. The fact that the pressor responses were similar in the two groups is also puzzling. One would predict an increased cardiovascular response in the absence of baroreceptor reflexes.

Another hormone thought to be involved in the regulation of salt and water balance is atrial natriuretic peptide, which is increased by both volume and osmotic stimuli. Its secretion is also affected by denervation, which results in a reduction in basal levels and the response to hypertonic saline. There is evidence that atrial natriuretic peptide may inhibit vasopressin and oxytocin secretion, particularly under stimulated conditions. Thus, the deficit of atrial natriuretic peptide after denervation may play a role in the change in neurohypophysal secretion. The net effects of hormones would be to conserve water and electrolytes and increase blood pressure.

The neural pathways by which the baroreceptor nerves influence the hypothalamus are not understood. Extensive immunohistochemical studies show that there are connections between the brainstem catecholaminergic centers and the paraventricular and supraoptic hypothalamic nuclei. The A2 noradrenergic center (nucleus tractus solitarii region) is thought to project primarily to the parvo-cellar regions of the paraventricular nucleus while the A1 region (ventrolateral medulla) innervates the magnocellular areas in the supraoptic and paraventricular nuclei. There are connections between the A2 and A1 regions so that visceral afferent information can be transmitted centrally to the neurosecretory cells. Work from our laboratory also shows that SAD produces changes in peptide and catecholamine content in these hypothalamic regions. Electrophysiological studies suggest that baroreceptor nerves specifically influence vasopressin, but not oxytocin neurons. Stimulation of the A1 region of the brainstem causes a specific activation of phasic-


**Key Words** • baroreceptors • oxytocin • vasopressin • osmotic regulation • blood pressure • pituitary gland
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Lithium agents is indicated because of demonstrated hypokalemia. They should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving ACE inhibitors.

Adverse experiences occurring in greater than 1% of patients treated with VASOTEC included hyperkalemia (see PRECAUTIONS), hypokalemia, angioedema, and rash. Rash or other dermatologic manifestations may occur. These symptoms have disappeared or lessened on discontinuation of the drug and/or VASOTEC may be resumed.

In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. In some patients treated only once daily the usual dose range of VASOTEC was 10 mg to 20 mg daily under dose medical supervision. In such patients, an increase in dosage or addition of another antihypertensive drug may be necessary.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.0%), back pain (1.0%), diarrhea (1.0%), cough (1.0%), and fever (1.0%).

Other serious clinical adverse experiences occurring in 0.1% to 1% of patients have included hyperkalemia or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or coronary accident, possible secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, peripheral edema, angina pectoris, anginal pain, and cyanosis. Available data from clinical trials of enalapril are insufficient to show that enalapril may be less effective or less safe than other ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

Urogenital: Hemoglobin and hematocrit were observed in 20% of patients. These increases were almost always reversible upon continued therapy of VASOTEC and/or other concomitant diuretic therapy, in such patients. renal function should be monitored during the first few weeks of therapy.

In lawsuits in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon continued therapy of VASOTEC and/or other concomitant diuretic therapy, in such patients. renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure have no apparent precipitating cause of their renal impairment. It is not possible to predict in advance which patients are at risk for renal impairment who are able to tolerate such adjuncts. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for acute renal failure, hypotension should be avoided until there is no evidence of active bleeding or active ulceration, unless calcium carbonate is indicated because of demonstrated hypokalemia. They should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving ACE inhibitors.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that lithium be administered with caution in patients receiving VASOTEC and serum lithium levels should be monitored closely.

Pregnancy – Category C: There was no teratogenic or embryotoxic effect in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Foetal weight was decreased in a dose-related manner in rats at 20 mg/kg/day or greater (41 times the maximum human dose). Foetal resorption was increased in rats at 20 mg/kg/day or greater (41 times the maximum human dose). Maternal toxicity was minimal at 20 mg/kg/day or greater (41 times the maximum human dose). Foetal toxicity was minimal at 20 mg/kg/day or greater (41 times the maximum human dose). Maternal toxicity was increased at 100 mg/kg/day or greater (100 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC* (Enalapril Maleate) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing Mothers: Milk is basic怯tory contains radiotracer following administration of *enalapril maleate. It is not known whether this drug is secreted in human milk. Caution should be exercised when VASOTEC is given to mothers who are breast-feeding. Pediatric Use: Safety and effectiveness in children have not been established.

Acute Angina: Angina has been reported in patients receiving VASOTEC and/or other concomitant diuretic therapy. In patients with duodenal ulcer disease. Available data from clinical trials of enalapril are insufficient to show that enalapril may be less effective or less safe than other ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.
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