Mechanism of Vasopressin-Induced Bradycardia in Dogs

By Sarla Varma, M.D., M.S., Bhuwaneshwar P. Jaju, M.D., and Krishna P. Bhargava, M.D., Ph.D.

ABSTRACT

In dogs anesthetized with intravenous chloralose, vasopressin was injected either intravenously or into the cerebral ventricles, and the cardiovascular effects were studied before and after stabilizing the arterial blood pressure, bilateral vagotomy, and transection of the cervical cord at the level of C2. Intravenous vasopressin caused a rise in arterial blood pressure and pronounced bradycardia. The bradycardia appeared to be partly due to a peripheral depressant action on the heart, probably resulting from coronary constriction and partly from reflex vagal stimulation resulting from the rise in arterial blood pressure. A direct stimulating action of vasopressin on the central cardioinhibitory neurons played only a minor role in the production of the bradycardia. Injections of vasopressin, into either a lateral or the fourth ventricle, produced an insignificant rise in arterial blood pressure but marked bradycardia. A peripheral effect of the vasopressin after its absorption into the bloodstream could be excluded as the cause of the bradycardia, since an injection of vasopressin into the cerebral ventricles produced diuresis, not antidiuresis. The bradycardia was more pronounced and occurred earlier when the vasopressin was injected into the fourth rather than into a lateral ventricle. The bradycardia produced by the injection of vasopressin into the cerebral ventricles could be almost fully accounted for by a central stimulating action on the cardioinhibitory neurons in the region of the vagal nuclei, which are closer to the fourth ventricle than to the lateral ventricles.

ADDITIONAL KEY WORDS

cardioinhibitory center  vagi
lateral ventricles  fourth ventricle  carotid sinus reflex
coronary constriction

Intravenous injection of vasopressin induces a rise in blood pressure and bradycardia in anesthetized and unanesthetized animals (1, 2). The pressor response is due to direct generalized peripheral vasoconstriction (3), but the mechanism of bradycardia is not clear. The vasopressin-induced bradycardia has been attributed to direct myocardial depression arising from coronary vasoconstriction (1, 4, 5), reflex activation of vagal efferent nerves to the heart through the cardioinhibitory center (4), or reflex inhibition of the cardioaccelerator mechanism (6). An action of vasopressin directly on the central cardio-regulatory neurons has not been excluded.

The present study was undertaken to determine whether there was a central component of the cardiovascular action of vasopressin; this was investigated by injection of vasopressin in the cerebral ventricles of dogs. A mechanical device was used to prevent the rise of systemic arterial pressure induced by intravenous vasopressin and so eliminate the reflex effects of baroreceptor stimulation on the cardio-regulatory neurons. Furthermore, attempts were made to study the efferent path of vasopressin-induced bradycardia by cutting the vagi high in the neck, transecting the cervical cord at C2, or both.

Methods

Forty-seven dogs of either sex weighing from 8
to 16 kg were used. They were anesthetized by intravenous injection of chloralose, 80 to 100 mg/kg (British Drug House). To eliminate the effects of alterations in respiration on the cardiovascular system, the animals were maintained on intermittent positive pressure ventilation. Arterial blood pressure was recorded from the left femoral artery with a mercury manometer on a smoked kymograph paper or by a Statham transducer on a Grass Polygraph Model 5. The heart rate was determined from lead II of the electrocardiogram. The blood pressure was stabilized by using a mechanical buffer system (7). The method of Bhargava and Tangri (8) was used to cannulate a lateral ventricle and that of Bartelstone et al. (9) to cannulate the fourth ventricle. The vasopressin (Pitressin, Parke, Davis & Co.) was injected in a volume not exceeding 0.25 ml. In some experiments with injections of vasopressin into a lateral ventricle, both ureters were cannulated and the urine volume was measured at intervals of 20 minutes for at least 3 hours after the injection. To avoid tachyphylaxis, only a single dose of vasopressin was given to any one dog. The results were analyzed statistically.

**Results**

**INTRAVENOUS INJECTIONS**

An intravenous injection of 2 units of vasopressin caused a rise in arterial blood pressure and a slowing of the heart. The rise began within 20 seconds of the injection, reached a maximum in about 2 minutes, and returned gradually to preinjection level in about 30 minutes. Bradycardia began within 30 seconds, was maximal in about 5 minutes, and lasted over 30 minutes. The results

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**TABLE 1**

**Effect of Vasopressin on Heart Rate and Arterial Blood Pressure of Dogs**

<table>
<thead>
<tr>
<th>State of animal</th>
<th>Vasopressin (units)</th>
<th>Route</th>
<th>No. of exps.</th>
<th>Max. change in blood pressure* (mm Hg)</th>
<th>Max. decrease in heart rate* (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>None†</td>
<td>L.V.</td>
<td>12</td>
<td>+2 ± 1.3</td>
<td>6 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>None†</td>
<td>F.V.</td>
<td>6</td>
<td>+3 ± 1.8</td>
<td>7 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>iv</td>
<td>12</td>
<td>+24 ± 3.1</td>
<td>48 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>L.V.</td>
<td>2</td>
<td>+7</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+6, +8)</td>
<td>(15 &amp; 19)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>L.V.</td>
<td>18</td>
<td>+6 ± 0.9</td>
<td>26 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>F.V.</td>
<td>4</td>
<td>−2</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(−1 to −4)</td>
<td>(33 to 48)</td>
</tr>
<tr>
<td>Stabilized blood</td>
<td>2.0</td>
<td>iv</td>
<td>6</td>
<td>+6 ± 1.4</td>
<td>36 ± 5.2</td>
</tr>
<tr>
<td>pressure</td>
<td>1.0</td>
<td>L.V.</td>
<td>2</td>
<td>None</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(30 &amp; 32)</td>
</tr>
<tr>
<td>Bilateral vagotomy</td>
<td>2.0</td>
<td>iv</td>
<td>5</td>
<td>+43 ± 11.3</td>
<td>30 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>L.V.</td>
<td>10</td>
<td>+4 ± 1.1</td>
<td>8 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>F.V.</td>
<td>2</td>
<td>None</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4 &amp; 8)</td>
</tr>
<tr>
<td>Transected spinal cord (C2)</td>
<td>1.0</td>
<td>L.V.</td>
<td>2</td>
<td>−8</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(−4, −12)</td>
<td>(16 &amp; 18)</td>
</tr>
<tr>
<td>Bilateral vagotomy</td>
<td>2.0</td>
<td>iv</td>
<td>5</td>
<td>+46 ± 8.1</td>
<td>30 ± 6.1</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>L.V.</td>
<td>3</td>
<td>+1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0 to +2)</td>
<td>(1 to 3)</td>
</tr>
</tbody>
</table>

L.V. = lateral ventricle; iv = intravenous; F.V. = fourth ventricle.

*Mean ± se. When number of experiments is less than 5, the range is given in parentheses.
†0.25 ml saline injected as control.
obtained in 12 dogs are summarized in Table 1. The mean maximal increase in arterial blood pressure was 24 mm Hg and the mean decrease in heart rate was 48 beats/min.

When the arterial blood pressure was stabilized by a "buffer device," an intravenous injection of 2 units of vasopressin caused only a small rise in blood pressure, but there was still pronounced slowing of the heart beat; the mean maximal decrease was 36 beats/min.

Bilateral vagotomy with or without transection of the cord at C5 did not diminish the pressor effect of an intravenous injection of 2 units of vasopressin, but the bradycardia was not as pronounced; the mean maximal decrease in heart rate was 30 beats/min.

INJECTIONS INTO A LATERAL VENTRICLE

Injection of 0.25 ml of saline solution into the lateral ventricle produced an insignificant rise in arterial blood pressure (2 mm Hg) and a mild bradycardia (6 beats/min) lasting about 15 minutes (Table 1).

An injection of 1 unit of vasopressin into the lateral ventricle caused only a slightly greater rise in arterial blood pressure than the control injection of saline solution, but caused bradycardia that was definite although less pronounced than after intravenous injections. Bradycardia began within 40 seconds of the injection and lasted 30 to 90 minutes. The results obtained on 18 dogs are summarized in Table 1. Injection of 0.05 units of vasopressin into the lateral ventricle in two dogs decreased heart rate by 15 beats in one and 19 beats in the other.

Stabilization of the blood pressure did not affect the bradycardia produced by an injection of 1 unit of vasopressin into the lateral ventricle. The mean maximal decrease in heart rate obtained in two experiments was 31 beats/min.

Bilateral vagotomy greatly reduced the effect of an intraventricular injection of 1 unit of vasopressin on heart rate. As shown in Table 1, spinal cord transection was not as effective as bilateral vagotomy in reducing the bradycardia produced by an injection of 1 unit of vasopressin into a lateral ventricle. After cord transection, the injections produced a mean maximal decrease in heart rate of 17 beats/min as compared to 8 beats/min after vagotomy. After bilateral vagotomy plus cord transection, the mean maximal decrease in heart rate produced by the vasopressin injections was only 2 beats/min.

By measuring the effect on urine volume it was shown that the cardiovascular effects produced by the injections of vasopressin into the lateral ventricle were not due to leakage of vasopressin into the circulation because the injections did not produce antidiuresis. On the contrary, a diuretic response was obtained (Fig. 2).

INJECTIONS INTO THE FOURTH VENTRICLE

Injections of 1 unit of vasopressin into the fourth ventricle had practically no effect on arterial blood pressure but caused bradycardia, which was more marked and began earlier than after an injection of the same dose into a lateral ventricle. Bradycardia began within 10 seconds of the injection, was maximal in about 15 minutes, and lasted for

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Diuretic effect of an injection of 1 unit of vasopressin into the lateral ventricle of dogs. Mean increase in urine output with standard error in nine dogs.

about 90 minutes. As shown in Table 1, the mean maximal decrease in heart rate was 39 beats/min; it was 26 beats/min after injection into a lateral ventricle. After bilateral vagotomy the injection of 1 unit of vasopressin produced little bradycardia.

Discussion

These results show that different sites of action are responsible for the bradycardia produced by intravenous vasopressin and that injected into the cerebral ventricles. The main mechanisms for the bradycardia after intravenous injection appear to be myocardial depression as a result of coronary constriction and reflex vagal inhibition as a result of a rise in arterial blood pressure. Vagal inhibition due to a central effect of vasopressin appears to be responsible for only a fraction of the pronounced bradycardia obtained with vasopressin given intravenously. In contrast, the bradycardia produced by vasopressin given intraventricularly, which was less pronounced than that after intravenous injection, appears to be almost fully accounted for by a central action.

The conclusions about the mechanisms responsible for the bradycardia produced by intravenous vasopressin were derived from a comparison of the cardiac effect produced by the same dose (2 units) injected intravenously under different conditions. Whereas in normal dogs the mean decrease in heart rate by such injections was 48 beats/min, it was only 36 beats when the rise in arterial blood pressure was prevented by a stabilizing device, and 30 beats/min when the vagi were cut, but there was no further reduction when the cervical cord was transected as well. Therefore, a direct action on the S-A node or myocardium appears to account for the decrease in heart rate of 30 beats/min. Vagal inhibition could account for a decrease of 18 beats/min, and the greater part of this inhibition, 12 beats/min, is brought about reflexly as a result of the rise in arterial blood pressure. Previous workers, too, suggested myocardial depression due to coronary constriction (1, 4, 5, 12) and reflex vagal inhibition due to the rise in arterial blood pressure (1, 4, 5, 10) as the main causes for the bradycardia produced by intravenous vasopressin. Although Youmans et al. (6) observed no effect of vasopressin on the denervated heart in situ, the myocardial depressant action resulting from coronary ischemia has been convincingly proved (12).

Absorption of vasopressin from the cerebrospinal fluid into the blood stream can be excluded as the cause of the bradycardia produced by its intraventricular injection, since this would have resulted in antidiuresis, whereas the injections into the cerebral ventricles produced diuresis, an effect previously observed by Nashold et al. (13, 14) in cats. Inhibition of release of endogenous antidiuretic hormone brought about by the high concentration of vasopressin in the cerebrospinal fluid may be the cause of this diuresis.

Bradycardia following an injection of vasopressin into the cerebral ventricles has hitherto been observed in man (15) and in
monkey (16) but the mechanism of its action has not been investigated. In cats, Nashold et al. (13) measured the blood pressure changes, but not heart rate after intraventricular injections of vasopressin.

The conclusion that the bradycardia produced by intraventricular injections of vasopressin is almost fully accounted for by a central stimulating action on the cardioinhibitory neurons reached by the vasopressin when penetrating the walls of the cerebral ventricles is based on the effects produced on the bradycardia by stabilizing the arterial blood pressure, cutting the vagi, and transecting the cervical cord. In intact dogs, the injection produced a small rise of arterial blood pressure, apparently insufficient to initiate reflex vagal inhibition because the vasopressin bradycardia remained unchanged when the rise was prevented by stabilizing the blood pressure. On the other hand, bilateral vagotomy nearly abolished the bradycardia, suggesting a central stimulating action on the cardioinhibitory neurons as the main factor responsible for the bradycardia of intraventricular vasopressin. Some additional central inhibitory action on the cardioaccelerator neurons is suggested by the findings that cervical cord transection somewhat reduced the bradycardia and that vagotomy with cord transection was more effective than vagotomy alone and abolished the bradycardia. Suppression of the cardioaccelerator mechanism had been suggested by Youmans et al. (6) as a contributory factor for the bradycardia produced by intravenous vasopressin; this could be a reciprocal suppression due to stimulation of the cardioinhibitory neurons.

A stimulating effect on the cardioinhibitory neurons located in the region of the vagal nuclei, which appear to be the site of action of vasopressin, readily explains why the bradycardia occurred earlier and was more pronounced after injection into the fourth, than after injection into a lateral, ventricle, because when injected into the fourth ventricle, the vasopressin will reach this region earlier and in higher concentration than when it is injected into a lateral ventricle.

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References


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