The Role of Vasopressin and the Sympathetic Nervous System in the Cardiovascular Response to Vagal Cold Block in the Conscious Dog

Eileen M. Hasser, Joseph R. Haywood, Alan Kim Johnson, and Vernon S. Bishop

SUMMARY. This study examined the role of arginine vasopressin in the pressor response to vagal cold block and evaluated a possible interaction between vasopressin and the sympathetic nervous system during vagal block in conscious dogs with (carotid sinus intact) and without (sinoaortic denervated) functional arterial baroreflexes. In both carotid sinus intact and sinoaortic denervated dogs, elimination of the arginine vasopressin pressor system by the specific vasopressin antagonist d(CH₂)₅Tyr(Me)AVP did not alter the response to vagal block, as evaluated by changes in arterial pressure. Subsequent removal of the sympathetic nervous system by ganglionic blockade abolished the response to vagal block. When ganglionic blockade was induced in the absence of the vasopressin antagonist, the pressor response to vagal block was reduced by only 60%. Arginine vasopressin antagonist after ganglionic blockade reduced the response to vagal block by an amount equivalent to 45% of the original increase in pressure. The effects of blockade of either vasopressin or the sympathetic nervous system on the pressor response to vagal block were significantly greater when the other system had previously been eliminated. Data suggest that both arginine vasopressin and the sympathetic nervous system contribute to the pressor response to vagal block. One interpretation of these results is that vasopressin also interacts centrally to inhibit sympathetic outflow and thus modulates the hemodynamic manifestation of interruption of vagal afferents. (Circ Res 55: 454–462, 1984)

CARDIOPULMONARY receptors with vagal afferents exert a tonic inhibitory influence on both sympathetic nervous system outflow and humoral factors involved in circulatory control. In particular, low pressure receptors have been shown to modulate plasma levels of arginine vasopressin (AVP), tonically inhibiting its secretion (Share and Levy, 1962; Clark and Rocha E Silva, 1967; Share, 1968; Thames and Schmid, 1979; Thames et al., 1980; Bishop et al., 1984). It is still uncertain, however, whether the hemodynamic manifestation of changes in cardiopulmonary reflex activity is the result of alterations in the sympathetic nervous system, in AVP, or is the net effect of an interaction between these systems.

Evidence indicates that AVP exerts a central nervous system interaction with the arterial baroreflex (Cowley et al., 1974; Montani et al., 1980; Liard et al., 1981; Guo et al., 1982; Undesser et al., 1984). Conscious dogs subjected to arterial baroreceptor denervation exhibit greatly enhanced pressor sensitivity to AVP which cannot be explained on the basis of loss of the buffering effects of the baroreceptors alone. It appears that AVP acts at some central nervous system site to inhibit sympathetic outflow and enhance parasympathetic activity.

Other evidence indicates that AVP may act as a neurotransmitter within the central nervous system (Sofroniew and Weidnl, 1978; Swanson and Sawchenko, 1980; Sawchenko and Swanson, 1981). AVP pathways impinging on medullary areas known to be important in cardiovascular control have been identified. This evidence, taken together, suggests that AVP may act within the central nervous system to modify the effects of afferent input from various cardiovascular reflexes.

In view of the evidence that AVP acts to augment the inhibitory influence of arterial baroreceptors, it seemed possible that the elevation in plasma AVP during vagal block might exert both vasoconstrictor effects and a central action that simultaneously inhibits sympathetic nervous system outflow. Such a role for AVP during interruption of vagal afferents is shown in Figure 1. Vagal block may increase both sympathetic nervous system activity and plasma AVP concentration. The elevated levels of AVP may then act in the central nervous system to inhibit the enhanced sympathetic outflow due to interruption of vagal afferents. The hemodynamic response to vagal block would then be the net result of changes in sympathetic activity, in plasma AVP levels, and a central interaction between these systems.

The present study was undertaken to determine whether the changes in plasma AVP which occur in response to interruption of vagal afferent input in the conscious dog contribute to the manifestation of
nerve trunk in the dog. This procedure also made it possible to achieve complete sinoaortic denervation by sectioning aortic arch afferents, which also traverse the vagal afferents from cardiopulmonary receptors without affecting baroreceptors. The aortic baroreceptors were denervated with isopropyl alcohol in order to denervate the aortic arch was stripped of all nerves and adventitia and painted with 30 mg Ag and maintained with halothane during surgery. Under sterile conditions, a left thoracotomy was performed through the 4th intercostal space. The aortic arch was stripped of all nerves and adventitia and painted with isopropyl alcohol in order to denervate the aortic arch baroreceptors. The aortic baroreceptors were denervated to ensure that bilateral vagal cold block interrupted vagal afferents from cardiopulmonary receptors without affecting aortic arch afferents, which also traverse the vagal nerve trunk in the dog. This procedure also made it possible to achieve complete sinoaortic denervation by subsequently denervating carotid sinus baroreceptors. A 17-gauge polyvinyl catheter was inserted in the descending aorta to measure arterial pressure, and exteriorized through the back of the neck.

Sinoaortic Denervation

One week after the initial surgery, 12 dogs were again anesthetized with sodium pentothal. An anterior cervical incision was made, and the carotid arteries isolated at the region of the carotid sinus. All nerves and tissue were stripped from the sinus, and from the carotid artery, and all branches several centimeters above and below the area of the carotid sinus (Bishop and Peterson, 1978; Peterson and Bishop, 1974). This region was then painted with isopropyl alcohol. This procedure resulted in complete baroreceptor denervation, as indicated by the elimination of reflex bradycardia in response to elevation of arterial pressure with phenylephrine (80 μg). These dogs were entered into the sinoaortic-denervated (SAD) group. A second group of eight dogs was not subjected to carotid sinus denervation, and was designated as the carotid sinus intact group.

Implantation of Vagal Cooling Coils

A midline cervical incision was made, and the carotid arteries and vagus nerves were isolated bilaterally. Coils were implanted according to the method previously described (Bishop and Peterson, 1978). The vagi were dissected according to the method previously described (Bishop and Peterson, 1978). The vagi were dissected free from the carotid arteries on both sides. We then isolated the carotids from the vagi by suturing a layer of muscle over them to insulate them from the effects of the cold during vagal block. A coil made of 10-gauge stainless steel tubing was placed around each vagus nerve. A piece of 18-gauge polyvinyl tubing with the distal end knotted was sutured to the inside of the coil. Thermistors could later be inserted into the coil via this tubing to monitor temperature. The nerve and coil were insulated from the surrounding tissue by placing a cylindrical piece of medical grade silastic rubber around each coil. The thermistor tubing and silastic tubing connected to each coil were exteriorized through the skin.

A 13-gauge polyvinyl catheter was placed in the jugular vein for injection of drugs. Dogs were allowed to recover for 7–10 days before experiments were initiated.

Experimental Protocol

Both carotid sinus intact and SAD dogs were subjected to two experimental protocols, which were conducted on separate days. All experiments were conducted while animals were conscious and lying unrestrained in a hammock. Arterial pressure and heart rate were monitored for 20–30 minutes prior to experimental manipulations to ensure a stable hemodynamic state. Bilateral cold block of the vagus nerves was then produced by circulating cold antifreeze (−16°C) through the coils around the vagi. Temperature within the coils was monitored via thermistors, and vagal block was assumed to be complete when the temperature reached 2°–0°C. Dogs were then allowed to recover for 20–40 minutes following vagal block.

The vascular vasopressin antagonist, [1-(β-mercaptopropionyl-β,β-cyclopentamethylene propionic acid)-2-(O-methyl)-tyrosine]-Arg⁴-vasopressin (d(CH₂)₅Tyr(Me)AVP) (10 μg/kg), was administered intravenously, and 10 minutes were allowed for stabilization of the hemodynamic response. Bilateral vagal cold block was repeated, followed by another recovery period. Animals then were subjected to

Methods

Mongrel dogs were anesthetized with sodium pentothal (30 mg/kg) and maintained with halothane during surgery. Under sterile conditions, a left thoracotomy was performed through the 4th intercostal space. The aortic arch was stripped of all nerves and adventitia and painted with isopropyl alcohol in order to denervate the aortic baroreceptors. The aortic baroreceptors were denervated to ensure that bilateral vagal cold block interrupted vagal afferents from cardiopulmonary receptors without affecting aortic arch afferents, which also traverse the vagal nerve trunk in the dog. This procedure also made it possible to achieve complete sinoaortic denervation by

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ganglionic blockade with hexamethonium (12 mg/kg) and atropine (0.05 mg/kg), and allowed a 10-minute stabilization period. Bilateral vagal cold block was again repeated.

On separate days, the same group of carotid sinus intact animals were subjected to the second protocol, which was similar to the first except that the order of administration of ganglionic blocking agents and AVP antagonist was reversed. Separate groups of SAD dogs were used for each protocol, with two of the animals from the first group of SAD animals being included in the second protocol.

At the end of each protocol, efficacy of ganglionic blockade was determined by lack of bradycardia to phenylephrine-induced increases in arterial pressure or lack of depressor and heart rate responses to veratrum alkaloids in carotid sinus intact and SAD animals, respectively. Efficacy of AVP blockade was confirmed by elimination of pressor responses to intravenously administered AVP.

Responses following AVP antagonist and ganglionic blockade together were similar, regardless of the order of administration. These results were therefore pooled for analysis.

To eliminate potential interactions with the renin-angiotensin system, the converting enzyme inhibitor captopril (1 mg/kg, iv) was administered to two carotid sinus intact and two SAD dogs, and the protocols repeated.

**Data Analysis**

The responses to vagal block under the different conditions were analyzed by two-way analysis of variance. Comparison of vagal block effects was carried out by one-way analysis of variance. Significant effects determined by analyses of variance were evaluated using Duncan's multiple range test. Effects of AVP antagonist and ganglionic blockade on responses to vagal block in the presence or absence of the other intervention were analyzed by Student's paired or unpaired t-test. A probability level of less than 0.05 was considered statistically significant.

**Results**

**Dogs with Intact Carotid Sinus Baroreceptors**

*Resting Hemodynamic Responses to Ganglionic Blockade and Vasopressin Antagonist*

In carotid sinus intact animals, ganglionic blockade significantly reduced arterial pressure by 14 ± 4 mm Hg, from 105 ± 6 to 91 ± 6 mm Hg. Following AVP antagonist administration, the depressor response to ganglionic blockade was significantly augmented. Arterial pressure fell from 103 ± 2 to 71 ± 5 mm Hg, a decrease of 32 ± 5 mm Hg. Ganglionic blockade significantly increased heart rate by 41 ± 7 and 23 ± 9 beats/min before and after AVP antagonist, respectively.

AVP antagonist had no significant effects on resting arterial pressure or heart rate when administered alone. During ganglionic blockade, however, AVP antagonist significantly decreased arterial pressure by 17 mm Hg, from 92 ± 7 to 75 ± 5 mm Hg. This effect was significantly greater than that observed prior to ganglionic blockade.

**Response to Bilateral Vagal Cold Block**

Prior to any interventions, resting mean arterial pressure and heart rate were 100 ± 5 mm Hg and 91 ± 2 beats/min, respectively. Responses to bilateral vagal cold block under control conditions, and after AVP antagonist and ganglionic blockade, are shown in Figure 2. Vagal block significantly elevated arterial pressure 21 ± 2 mm Hg and heart rate 74 ± 13 beats/min. Whereas vagal block interrupts both vagal afferent and efferent activity, the arterial pressure response has been shown to be due to vagal afferents, since blockade of vagal efferent effects with atropine does not alter the pressor response to vagal block (Bishop and Peterson, 1978). As mentioned above, administration of AVP antagonist did not alter resting blood pressure or heart rate. After AVP blockade, interruption of vagal afferents increased arterial pressure 22 ± 2 mm Hg, and heart rate 82 ± 13 beats/min, responses which were not different from control. Subsequent ganglionic blockade eliminated both the tachycardia and the pressor response to vagal block.
In six dogs in which ganglionic blockade was established prior to AVP antagonist, resting arterial pressure and heart rate were 108 ± 7 mm Hg and 87 ± 8 beats/min, respectively. Figure 3 depicts the responses to vagal cold block in these animals. Vagal block alone significantly increased arterial pressure 24 ± 3 mm Hg and heart rate 51 ± 10 beats/min. Following ganglionic blockade, the pressor response to vagal block was significantly reduced to 11 ± 1 mm Hg and the tachycardia eliminated. Subsequent administration of AVP antagonist abolished the remaining pressor response to vagal block. The response to vagal block in two animals was different from that in the other six dogs. In these dogs, ganglionic blockade enhanced the pressor response to vagal block from 26 to 41 mm Hg. This enhanced response was due to AVP, because it could be prevented by pretreatment with AVP antagonist and could be reversed by administration of AVP antagonist during the elevation in pressure due to vagal block. In one of these animals, the response to vagal cold block after AVP antagonist alone was similar to that of the other dogs. In the other animal, however, the entire pressor response to vagal block appeared to be due to AVP, because it was eliminated after AVP antagonist alone.

Figure 4 illustrates the relative effects of AVP antagonist on the responses to vagal block when administered alone or after ganglionic blockade. Data are expressed as a percentage of the original vagal block response. AVP antagonist alone had no significant effect on either the arterial pressure or heart rate response to vagal cold block. After ganglionic blockade, however, AVP antagonist significantly reduced the pressor response by 11 ± 1 mm Hg, or 46 ± 9% of the original response. This effect of AVP antagonist after ganglionic blockade was significantly greater than that observed when only AVP was inhibited. No significant heart rate effects were observed.

Relative effects of ganglionic blockade alone or in...
the presence of AVP antagonist are shown in Figure 5. Ganglionic blockade alone significantly reduced the pressor response to vagal block by 13 ± 2 mm Hg, or 51 ± 6% of the response, and abolished the tachycardia. After AVP antagonist, the pressure elevation was diminished by 23 ± 2 mm Hg, or 91 ± 9% of the original response. This effect of ganglionic blockade following AVP antagonist was significantly greater than that observed when administered alone. Ganglionic blockade always eliminated the tachycardia due to vagal block. Because the heart rate response to vagal block was augmented after AVP antagonist, subsequent ganglionic blockade reduced the tachycardia by an amount equal to 147 ± 26% of the original heart rate rise.

Sinoaortic Denervated Dogs

Resting Hemodynamic Responses to Ganglionic Blockade and Vasopressin Antagonist

In SAD animals, when ganglionic blockade was affected prior to other interventions, arterial pressure decreased significantly from 97 ± 2 to 77 ± 3 mm Hg, a change of 20 ± 3 mm Hg. In animals in which ganglionic blockade was induced after administration of the AVP antagonist, resting arterial pressure was decreased from 96 ± 3 to 75 ± 7 mm Hg by ganglionic blockade. This reduction of 21 ± 5 mm Hg in resting arterial pressure was not significantly different from that due to ganglionic blockade prior to AVP antagonist. Heart rate was not significantly altered in either case.

AVP antagonist alone resulted in a small but significant reduction in resting arterial pressure of 7 ± 3 mm Hg in SAD dogs. When AVP antagonist was administered after ganglionic blockade, pressure fell significantly by 12 ± 4 mm Hg, from 78 ± 6 to 66 ± 7 mm Hg. The effect of AVP antagonist alone on resting arterial pressure was not significantly different from that observed when AVP antagonist was administered subsequent to ganglionic blockade. Heart rate was not altered by AVP blockade in either case.

Response to Bilateral Vagal Cold Block

In the group of animals in which AVP antagonist was administered prior to ganglionic blockade, resting mean arterial pressure and heart rate were 99 ± 5 mm Hg and 121 ± 8 beats/min, respectively. Bilateral vagal cold block significantly elevated arterial pressure 54 ± 7 mm Hg and heart rate 42 ± 7 beats/min (Fig. 6). After administration of AVP antagonist, the elevations in arterial pressure (52 ± 10 mm Hg) and heart rate (46 ± 8 beats/min) due to vagal block were similar in magnitude to those under control conditions. When ganglionic blockade was induced subsequent to AVP antagonist, the response to vagal block was abolished.

In the group of animals in which ganglionic blockade preceded AVP antagonist, resting mean arterial pressure and heart rate were 88 ± 7 mm Hg and 105 ± 7 beats/min, respectively. Vagal block significantly increased arterial pressure 70 ± 10 mm Hg and heart rate 56 ± 14 beats/min (Fig. 7). After administration of the ganglionic blocking agent, the pressor response to vagal block was significantly reduced to 27 ± 4 mm Hg, and the heart rate response abolished. AVP antagonist after ganglionic blockade eliminated the remainder of the blood pressure response.

The 60% reduction in the pressor response to vagal block due to ganglionic blockade alone was significantly less than the effect of ganglionic block to reduce the vagal block response when induced in the presence of the AVP antagonist. Similarly, the effect of AVP antagonist to diminish the increase in arterial pressure during vagal block was significantly greater when the antagonist was administered during ganglionic blockade than when it was administered alone.

In one SAD and two carotid sinus intact dogs, AVP antagonist was administered at the peak of the

![Figure 5. Effects of ganglionic blockade on the arterial pressure and heart rate responses to vagal block before and after AVP antagonist](http://circres.ahajournals.org/)

*P < 0.05.
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**FIGURE 6.** Change in mean arterial pressure (top panel) and heart rate (bottom panel) due to bilateral vagal cold block under control conditions, after administration of AVP antagonist, and after both AVP antagonist and ganglionic blockade in conscious sinoaortic denervated dogs (n = 7). Results were analyzed by one-way analysis of variance and Duncan’s multiple range test. *P < 0.05.

**FIGURE 7.** Change in mean arterial pressure (top panel) and heart rate (bottom panel) due to bilateral vagal cold block under control conditions, after ganglionic blockade, and after both ganglionic blockade and AVP antagonist in conscious sinoaortic denervated dogs (n = 7). Results were analyzed by one-way analysis of variance and Duncan’s multiple range test. *P < 0.05.

pressure elevation during vagal block after ganglionic blockade. In all cases, arterial pressure fell to a level either equal to or below the pressure immediately prior to the initiation of vagal block, despite continued cooling of the vagi. Subsequent vagal block produced no response.

To determine whether the pressure elevation during vagal block after AVP antagonist was due partially to activation of the renin-angiotensin system, four animals were administered the converting enzyme inhibitor, captopril. Captopril did not alter the response to vagal cold block.

**Discussion**

The data from this study indicate that both AVP and the sympathetic nervous system contribute to the excitatory response to interruption of cardiopulmonary vagal afferents. In addition, AVP appears to interact with the sympathetic nervous system in mediating the reflex response to bilateral vagal cold block. The failure of AVP antagonist alone to affect the response to vagal block suggests that AVP was not involved in the elevation of blood pressure when the sympathetic nervous system was intact. However, when the sympathetic nervous system was effectively removed by ganglionic blockade, AVP was capable of producing approximately 45% of the initial response to vagal block. Similarly, when ganglionic blockade was induced in the absence of AVP antagonist, the sympathetic nervous system appeared to be responsible for approximately 60% of the initial pressor response to vagal block. When AVP had been eliminated by prior administration of the antagonist, however, sympathetic activation appeared to mediate the entire pressor response to vagal block. Thus, both the sympathetic nervous system and AVP were capable of producing a pressor response during interruption of vagal afferents. In addition, each system seemed to play a more powerful role in the excitatory response to vagal block when the other system was removed, indicating an interaction between the two systems.

One possible explanation for the relative effects observed with AVP antagonist involves sympathetically mediated activation of the renin-angiotensin
AVP interacts with the cardiovascular control system. Under control conditions, increases in sympathetic outflow in response to vagal block could stimulate renin release (Donald, 1979), while the elevation in plasma AVP levels may act to inhibit the sympathetically mediated increase in renin (Shade et al., 1973). After AVP antagonist, renin levels could increase during vagal block and contribute to the pressor response, balancing the removal of the pressor effects of AVP. However, two lines of evidence argue against this possibility. Previous work by Mursch and Bishop (1980) indicates that plasma renin levels are not elevated by vagal cold block in the conscious dog under control conditions when renal perfusion pressure is allowed to increase. Second, in this study, administration of the converting enzyme inhibitor, captopril, did not alter the response to vagal block after AVP antagonist, indicating that angiotensin was not playing a role in the pressure rise.

Arterial baroreceptors are stimulated during vagal cold block, acting to oppose both the increase in arterial pressure and the elevation in plasma AVP levels during vagal block. Because arterial pressure was increased to a lesser extent by vagal cold block after ganglionic blockade, it is possible that, under these conditions, plasma AVP concentration might increase to a greater extent. Greater elevations in plasma AVP concentration could then account for the enhanced effects of AVP antagonist on the vagal block response after ganglionic blockade. However, such a mechanism could not be involved in SAD dogs. Thus, it appears that the observed enhancement of the effects of AVP antagonist or ganglionic blockade on the pressor response to vagal block in the presence of the other intervention is not dependent on functional baroreceptors. Since relative responses to vagal block following ganglionic blockade and AVP antagonist were similar in six carotid sinus intact dogs and in SAD animals, it appears that this mechanism alone is not operating even in carotid sinus intact dogs. In addition, the elevation in plasma AVP during vagal block is significantly greater in SAD than in carotid sinus intact dogs (Bishop et al., 1984). If the pressor response to vagal block after elimination of sympathetics was due only to greater AVP levels in carotid sinus intact animals, it would be expected that AVP antagonist alone would diminish the pressor response to vagal block in SAD dogs, in which plasma AVP is elevated from 4.4 ± 1.0 to 33.4 ± 4.8 μU/ml during vagal block (Bishop et al., 1984). This, however, was not the case. The response to vagal block was not altered by AVP antagonist alone in either carotid sinus intact or SAD dogs, but AVP antagonist eliminated the remaining increase in pressure due to vagal block after ganglionic blockade.

The data in the present study suggest an interaction of AVP with cardiopulmonary reflexes. A large body of evidence is accumulating to suggest that AVP interacts with the cardiovascular control system of other reflexes, particularly the arterial baroreflexes (Cowley et al., 1974; Montani et al., 1980; Liard et al., 1981; Guo et al., 1982). Cowley et al. (1974) and Montani and colleagues (1980) suggested that AVP interacts with the baroreflex in the conscious dog so as to enhance the inhibitory effects of the reflex. The inhibitory action of AVP appears to be particularly pronounced when it is infused into the vertebral arteries in the dog, indicating that AVP interacts with the baroreflex at some central site perfused by the vertebral arteries (Liard et al., 1981). These central inhibitory effects of AVP are abolished by denervation of the arterial baroreceptors, suggesting that they are dependent directly upon functional arterial baroreflexes. More recent studies confirmed the enhancement of baroreceptor inhibition of sympathetic outflow in the rabbit (Guo et al., 1982; Undesser et al., 1984), since inhibition of lumbar or renal sympathetic nerve activity in response to similar increases in arterial pressure is greater when pressure is altered by infusion of AVP than when altered by phenylephrine. The site of this central action of AVP to enhance baroreceptor inhibition of renal sympathetic nerve activity in the conscious rabbit was localized to the area postrema (Undesser et al., 1984).

Other evidence also indicates that AVP may be acting at some site in the central nervous system to affect cardiovascular function. Neuroanatomical data indicate that there is a reciprocal afferent-efferent link between AVP-containing cells of the paraventricular nucleus of the hypothalamus and regions of brainstem and spinal cord which are involved in autonomic regulation of the cardiovascular system (Swanson and Sawchenko, 1980; Sawchenko and Swanson, 1981). AVP also affects catecholamine turnover in brain regions which appear to be involved in circulatory function (Tanaka et al., 1977; Versteeg et al., 1979). Finally, administration of exogenous AVP appears to modify central aspects of cardiovascular control, associated with both inhibitory and excitatory hemodynamic responses. Exogenous AVP has generally been shown to exert inhibitory effects on the cardiovascular system, whether administered systemically or intracerebroventricularly (Youmans et al., 1952; Varma et al., 1969; Cowley et al., 1974; Bohus, 1974; Montani et al., 1980; Liard et al., 1981). Nevertheless, when administered by microinjection into the nucleus tractus solitarius of the rat, AVP increased arterial pressure and heart rate (Matsuguchi et al., 1982). However, an inhibitory interaction of AVP with the arterial baroreflex could not be demonstrated in this species (Sharabi et al., 1982), suggesting that the central effects of AVP may be different in the rat. In most species, therefore, it appears that AVP has the capacity to modulate central nervous system control of the circulation, and that this modulation is generally inhibitory in nature.

Although sympathetic activity was not directly...
measured, data from the present study suggest that a central inhibitory interaction may exist between AVP and the sympathetic nervous system during interruption of vagal afferent nerves. Such an interaction has been depicted in Figure 1. Bilateral vagal cold block removes the tonic inhibitory influence of vagal afferents, resulting in enhanced sympathetic outflow and elevated plasma AVP concentration. The elevated levels of plasma AVP, together with sympathetic activation, may contribute to the arterial pressure response to vagal block. However, based upon our data, we postulate that AVP may act at some central site to reduce sympathetic activity, thus simultaneously blunting the vasoconstrictor response to vagal block. Therefore, assuming that the AVP antagonist blocks the effects of AVP at both the vasculature and at this central site, its administration alone would have little or no effect on the excitatory response to vagal block as evaluated by changes in arterial pressure. After AVP antagonist, the vasoconstrictor action of AVP would be eliminated, tending to reduce the pressure elevation, but sympathetic outflow would be augmented, enhancing the pressor response, and the net effect of AVP blockade would be only a small change in response. The pressure rise now would be mediated entirely by the enhanced levels of sympathetic nervous system activity. Thus, as found in our study, ganglionic blockade induced following AVP antagonist would abolish the entire pressor response to vagal block.

When ganglionic blockade is established alone, it should diminish the elevation in pressure due to vagal block. Under these conditions, neither sympathetic activation nor its inhibition by AVP should play a role in the pressor response to vagal cold block. The remaining pressor response would be due to AVP, unmasking its vasoconstrictor effects. This concept is also in agreement with the results obtained in this study, because after ganglionic blockade, approximately 45% of the initial pressor response remained and was subsequently eliminated by AVP antagonist.

The data from these experiments do not provide any evidence as to where the postulated central interaction might occur. The work of Liard (1981), however, suggests that the interaction of AVP with the arterial baroreflex occurs at some site in the hindbrain. Recent work (Undesser et al., 1984) indicates that AVP augments arterial baroreceptor inhibition of renal sympathetic nerve activity by an action at the area postrema. It therefore seems reasonable to speculate that this might be true also of the cardiopulmonary reflex. The area postrema is the only area in the hindbrain which is devoid of a blood-brain barrier. In addition, it has been shown that another peptide hormone, angiotensin II, acts at the area postrema to enhance sympathetic outflow (Ferrario et al., 1972). It therefore seems reasonable to consider the area postrema as a potential site for the interaction of AVP with the cardiopulmonary reflex.

Several points should be stressed regarding the diagram in Figure 1. First, the central interaction which is proposed is one involving AVP and the cardiopulmonary baroreflex. Other work has indicated that AVP may also interact with the arterial baroreflexes (Cowley et al., 1974; Montani et al., 1980; Liard et al., 1981; Guo et al., 1982; Undesser et al., 1984), and this work suggests that the central effects of AVP are dependent upon the arterial baroreflexes. However, it should be noted that the perturbations used in these studies were specifically designed to stimulate arterial baroreceptors. In the present study, vagal afferent activity was specifically altered, and it appeared that AVP also interacts centrally with this reflex. The central interaction of AVP with the cardiopulmonary baroreflex system appeared to be independent of functional arterial baroreflexes, because similar results were obtained in carotid sinus intact and SAD dogs. However, it is possible that arterial baroreceptors may influence the magnitude of the interaction by altering the levels of circulating AVP during vagal block. Second, most of the work regarding AVP and the arterial baroreflex has centered around the administration of exogenous AVP, the effects of which have been examined by stimulation of the inhibitory side of the reflex. In the present study, vagal afferent input was reduced and the effects of endogenously released AVP on the excitatory aspects of the reflex were evaluated. It appears that AVP endogenously released through a reflex response is able to act within the central nervous system to modulate that response.

The data from this study suggest that the elevation in AVP which occurs in response to bilateral vagal cold block contributes to the comitant pressor response. It also appears that there is an interaction between AVP and the sympathetic nervous system during vagal block such that the apparent contribution of one system to the pressor response is greater in the absence of the other system. Although further investigation directly examining sympathetic activity is required, the data from this study can be interpreted to mean that AVP may exert a central inhibitory action on the augmentation of sympathetic outflow due to interruption of vagal afferent activity.

We gratefully acknowledge the expert technical assistance provided by Linda Stahl and Judith Smith, and thank Terri Mason for her assistance in statistical analysis, and Janet Wall for typing the manuscript.

Supported by National Institutes of Health Grant No. HL-12415.

Dr. Johnson was a Visiting Professor from the Department of Psychology and the Cardiovascular Center, University of Iowa, Iowa City, Iowa, during the time this work was carried out.

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References


INDEX TERMS: Vasopressin • Vagal cold block • Cardiopulmonary reflexes • Reflex control of vasopressin • Interaction of vasopressin • Sympathetic
The role of vasopressin and the sympathetic nervous system in the cardiovascular response to vagal cold block in the conscious dog.
E M Hasser, J R Haywood, A K Johnson and V S Bishop

doi: 10.1161/01.RES.55.4.454

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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