Cardiovascular Actions of Vasopressin at the Ventrolateral Medulla

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Vasopressin acts at a number of sites in the central nervous system to alter arterial pressure. This study investigated the hypothesis that vasopressin acts at the rostral ventrolateral medulla to increase arterial pressure. The rostral pressor area of the medulla oblongata was exposed in urethane-anesthetized rats prepared for topical application of vasopressin. A 3-minute application of vasopressin (range 10^{-8} to 10^{-3} M) produced dose-dependent increases in arterial pressure that averaged between 2±1 and 65±11 mm Hg (p<0.01). Tachycardia was not a consistent response at any concentration of vasopressin. Intravenous administration of a V$_1$ vasopressin antagonist did not modify the pressor response produced by topical application of vasopressin (10^{-4} M). Application of the V$_1$ antagonist to the rostral pressor area, however, prevented the production of a pressor effect to subsequent topical application of vasopressin (10^{-4} M). These experiments suggest that vasopressin stimulates the activity of vasomotor neurons in the rostral ventrolateral medulla by a mechanism that involves a neuronal V$_1$ receptor. (Hypertension 1990;15(suppl I):I-102-I-106)
Results

Topical application of VP to the RVL of the rat produced dose-dependent increases in mean arterial pressure (MAP). Figure 1 shows that the lower doses of VP (10^{-8} and 10^{-7} M) did not significantly alter the baseline blood pressure. VP, in concentrations from 10^{-6} M to 10^{-3} M, however, produced significant increases (p<0.01) in arterial pressure. VP, throughout this dose range (10^{-8} to 10^{-3} M), did not alter heart rate consistently (Figure 1). Because four different doses of VP were applied in random order in each rat, we examined whether variations in blood pressure affected the response to topical application of VP. Table 1 lists the baseline values of MAP and heart rate in rats receiving no previous treatment with a VP antagonist. Multiple comparison of the values for MAP did not show any differences in baseline blood pressure, whereas analysis of variance demonstrated that VP doses had a significant effect on the increase in MAP (F=22.0, p<0.0001). Also shown in Table 1 is the fact that significant differences existed among the baseline values of heart rate before application of the peptide. Analysis of variance, however, demonstrated that application of VP at various concentrations did not significantly alter heart rate. Topical application of VP produced a pressor response with a characteristic time course. Figure 2A illustrates that topical application of VP (10^{-4} M) initiated an increase in blood pressure within 60 seconds after placement of the pledget on the ventral surface. By 4 minutes, MAP had increased by 50 mm Hg. This pressor response outlasted the removal of the pledget from the ventral surface. At higher VP concentrations (10^{-4} and 10^{-3} M), the pressor response lasted for as much as 15 minutes after application of the peptide to the ventral surface.

To elucidate whether the pressor response produced by topical application of VP to the ventral medulla was the result of leakage of the peptide into the systemic circulation, six rats were pretreated with the VP, VP antagonist. Adequacy of VP blockade was confirmed by elimination of the pressor response produced by intravenous bolus injection of 10^{-4} M VP. Figure 2B illustrates the pressor response produced by topical application of the peptide (10^{-4} M) in a rat that had been given the VP antagonist intravenously. The central pressor effect of VP in this rat pretreated with the VP antagonist was essentially the same as that obtained in a rat with no previous exposure to the VP antagonist (Figure 2A). In the group of rats that received the VP antagonist intravenously, there was a trend for MAP to decrease and heart rate to increase (see data in bottom row of Table 1). Comparison of the baseline values of MAP and heart rate for the two
groups of rats that subsequently received topical application of VP at $10^{-4}$ M concentration, however, did not reveal any difference in the baseline values of these variables whether the rats were untreated or pretreated with the $V_1$ VP antagonist intravenously. VP ($10^{-4}$ M), applied topically to the ventral medulla of rats ($n=6$) given the $V_1$ antagonist intravenously, produced an average increase in blood pressure of $35\pm3$ mm Hg ($p<0.01$). This pressor response was not different from the increase in blood pressure ($35\pm4$ mm Hg) obtained in a separate group of untreated rats ($n=6$). Topical application of VP during blockade of the peripheral $V_1$ VP receptors, however, was associated with a significant increase in heart rate ($46\pm5$ beats/min; $p<0.01$), which was not observed in untreated rats ($32\pm13$ beats/min; $p>0.05$).

To further establish the mode of action of VP at the ventral medulla, four of six rats that had received the $V_1$ antagonist intravenously were treated with the $V_1$ antagonist ($10^{-5}$ M) applied topically to the ventral medulla for 3 minutes. VP was applied topically a second time, immediately after removal of the antagonist from the ventral surface. Before application of the VP antagonist to the ventral medulla, this group of rats had baseline values of $60\pm3$ mm Hg for MAP and $440\pm25$ beats/min for heart rate. The antagonist did not alter the baseline blood pressure ($69\pm5$ mm Hg, $p>0.01$), whereas, the $V_1$ antagonist was associated with a significant increase in heart rate to $75\pm20$ beats/min ($p<0.05$). The topical application of the peptide during peripheral $V_1$ blockade increased MAP by $36\pm4$ mm Hg ($p<0.01$). The second application of the peptide, however, did not significantly increase MAP ($+5\pm2$ mm Hg, $p>0.10$). Blockade of ventral medullary $V_1$ VP receptors had a similar effect on heart rate. Before central VP blockade, topical application of VP increased heart rate by $57\pm7$ beats/min ($p<0.01$); whereas, after central VP blockade, topical application of the active peptide was without effect ($+6\pm3$ beats/min; $p>0.10$).

An additional group of rats received hexamethonium chloride (9 mg/kg i.v.) to assess the contribution of the sympathetic nervous system to the VP-induced pressor response. With the sympa-
ventral medulla, Keeler et al. have shown that ventral medulla as well as at more deeply located sites would not explain the observed responses because this would have to occur at very low concentrations of the peptide.

Although we did not assess the penetration of topically applied VP into the neural substrate of the ventral medulla, Keeler et al. observed maximal depressor or pressor responses to topical application of \( \gamma \)-aminobutyric acid (GABA) and bicuculline, respectively. Although we did not assess the penetration of topically applied VP into the neural substrate of the ventral medulla, Keeler et al. observed maximal depressor or pressor responses to topical application of \( \gamma \)-aminobutyric acid (GABA) and bicuculline, respectively. Although we did not assess the penetration of topically applied VP into the neural substrate of the ventral medulla, Keeler et al. observed maximal depressor or pressor responses to topical application of \( \gamma \)-aminobutyric acid (GABA) and bicuculline, respectively.

The contention that VP had a primary central action is supported by the finding that peripheral administration of a \( V_1 \) VP antagonist did not attenuate the pressor effect of the peptide. The fact that blockade of systemic \( V_1 \) VP receptors did not affect the pressor response to topical application of the peptide would be consistent with the notion that VP did not act at a lower brainstem site to promote significant release of VP from the neurohypophysis. A central site of action is also reinforced by the demonstration that topical application of the \( V_1 \) antagonist before application of VP prevented the pressor response. This observation suggests that VP acts at a \( V_1 \) receptor. A brain \( V_1 \) receptor has been implicated in the production of neurogenic cardiovascular actions of VP at the nucleus tractus solitarius (NTS) and spinal cord.

Data suggest that neuronal elements of the VLM might be sensitive to localized ischemia. Evidence, however, would weigh against the idea that topical application of VP elicits a sympathetically mediated response secondary to local ischemia of the ventral medulla. First, systemic administration of the \( V_1 \) antagonist did not alter the pressor response to topically applied VP. Second, Lassof and Altura showed that local application of VP to pial arterioles of anesthetized rats does not change microvascular diameter or blood flow. Additionally, Katsu- sic et al. showed that VP in a dose range of \( 10^{-10}-10^{-6} \) M produced a concentration-dependent relaxation of canine basilar artery rings that had been contracted by prostaglandin \( E_2 \). The possibility of a local vascular effect of VP in the ventral medulla is not ruled out because Long et al. have shown that intrathecal VP (10–100 pmol) caused significant reductions in lumbosacral spinal cord blood flow. Further, this effect of VP on spinal cord blood flow was blocked by the \( V_1 \) antagonist.

Preliminary experiments were performed to define the autonomic pathway involved in the pressor response of VP. After ganglionic blockade, topical application of VP had no influence on blood pressure or heart rate. Thus, it would seem that sympathetic activation is an important component of the pressor response produced by topical application of VP to the ventral medulla. In this regard, our results bear similarity to the involvement of the sympathetic nervous system in the pressor response produced by intrathecal injection of VP in anesthetized rats. Because the topically applied VP would be at highest concentrations at the ventral surface of the medulla in our experiments, it is probable that VP acts at sympathoexcitatory neurons of the VLM to increase arterial pressure. One of the interesting observations of this study was the absence of a reflex decrease in heart rate when VP was applied to the ventral medulla. This might be the outcome of a complex set of pathways having competing effects toward sympathoexcitatory neurons of the VLM. It is possible that the VP applied topically to the ventral medulla excited sympathoexcitatory neurons of the VLM, and this excitatory influence counteracted an inhibitory drive from baroreceptor reflex pathways originating in the NTS. Another consideration is that some of the VP applied to the ventral medullary surface gained access to the dorsomedial medulla where it would have to act at very low concentrations to attenuate baroreceptor reflex-mediated bradycardia. This mode of action would be consistent with the dem-
onstration of Michelini and Bonagamba15 that microinjection of VP into the medial NTS attenuated baroreceptor reflex bradycardia associated with pressor infusions of phenylephrine. Our data also suggest that VP receptors at sites lacking a blood–brain barrier might contribute to the responses produced by topical application of the peptide in the presence of the V1 VP antagonist. These observations implicate a physiological role for VP at the VLM, the data are pertinent to the observation of Porter and Brody18 who showed that lidocaine or kainic acid injection into the VLM substantially attenuated the hindquarter vasoconstriction and increase in blood pressure produced by stimulation of the paraventricular nucleus of the hypothalamus.

This study is the first demonstration that VP acts at the ventral medulla to influence blood pressure. In this regard, the ventral medulla as well as the NTS,9 locus coeruleus,19 and spinal cord10,11 are sites where VP acts to modulate cardiovascular function. Although the direct effect of VP on “cardiovascular” neurons was beyond the scope of the present study, one might suggest the peptide has excitatory effects similar to those found for lateral horn cells of the spinal cord.20,21 In a number of studies,8,9,21 the excitatory effects of VP have been successfully blocked by the central administration of the V1 antagonist. These observations implicate a V1 receptor as mediating these effects.

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