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Arginine Vasopressin Enhances Sympathetic Constriction Through the V₁ Vasopressin Receptor in Human Saphenous Vein

Pascual Medina, PhD; Antonio Acuña, BSc; Juan B. Martínez-León, MD; Eduardo Otero, MD;
José M. Vila, PhD; Martín Aldasoro, MD; Salvador Lluch, MD

Background—Arginine vasopressin (AVP) not only acts directly on blood vessels through V_1 receptor stimulation but also may modulate adrenergic-mediated responses in animal experiments in vivo and in vitro. The aim of the present study was to investigate whether AVP can contribute to an abnormal adrenergic constrictor response of human saphenous veins.

Methods and Results—Saphenous vein rings were obtained from 32 patients undergoing coronary artery bypass surgery. The vein rings were suspended in organ bath chambers for isometric recording of tension. AVP (3×10^{-9} mol/L) enhanced the contractions elicited by electrical field stimulation at 1, 2, and 4 Hz (by 80%, 70%, and 60%, respectively) and produced a leftward shift of the concentration-response curve to norepinephrine (half-maximal effective concentration decreased from 6.87×10^{-7} to 1.04×10^{-7} mol/L; $P < .05$). The V_1 vasopressin receptor antagonist d(CH₂)₅Tyr(Me)AVP (10^{-6} mol/L) prevented the potentiation evoked by AVP. The selective V_1 receptor agonist [Phe,² Orn⁸]-vasotocin (3×10^{-9} mol/L) induced potentiation of electrical stimulation–evoked responses, which was also inhibited in the presence of the V_1 receptor antagonist (10^{-6} mol/L). In contrast, the V_2 receptor agonist desmopressin (10^{-9} to 10^{-7} mol/L) did not modify neurogenic responses, and the V_2 receptor antagonist [d(CH₂)₅, D-Ile,² Ile,⁴ Arg⁸]-vasopressin (10^{-8} to 10^{-6} mol/L) did not prevent the potentiation induced by AVP. The dihydropyridine calcium antagonist nifedipine (10^{-6} mol/L) did not affect the potentiating effect of AVP.

Conclusions—The results suggest that low concentrations of AVP facilitate sympathetic neurotransmission and potentiate constrictor effects of norepinephrine in human saphenous veins. These effects appear to be mediated by V_1 receptor stimulation and are independent of calcium entry through dihydropyridine calcium channels. Thus, AVP may contribute to vascular mechanisms involved in acute ischemic syndromes associated with venous grafts, particularly if the sympathetic nervous system is activated. (***Circulation.*** 1998;97:865–870.)

Key Words: veins ■ arginine vasopressin ■ electrical stimulation ■ norepinephrine

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Arginine vasopressin (AVP) is a neuropeptide that promotes reabsorption of water in renal tubular cells through V_2 receptors and produces constriction of vascular smooth muscle through V_1 receptors.[1–3] In human vessels, AVP causes powerful V_1 receptor–mediated constriction in isolated mesenteric,[4,5] cerebral,[6,7] and renal[8] arteries. This effect is endothelium independent and due to direct stimulation of receptors located on smooth muscle cells.[5,9,10] Further studies of the physiological effects of AVP have implicated a possible role of V_2 receptors in mediating vasodilation in some vascular beds.[11–14]

AVP may also modify the effects of other vasoactive substances that are found in plasma or released from perivascular nerve endings. Several studies in various animal species have reported a significant augmentation by AVP of the vasoconstricting action of catecholamines.[15–17] However, in other studies, AVP did not change the constrictor activity of the peripheral sympathetic nervous system.[18] In the human forearm, AVP attenuates phenylephrine-induced vasoconstriction,[19] whereas recent experiments in human isolated mesenteric arteries show that AVP enhances adrenergic-mediated responses.[20] Currently, there is no information concerning the modulating effects of AVP on human veins. A recent report from our laboratory indicates that AVP exerts low contractile effects on human saphenous veins compared with human arteries,[21] thus suggesting that these veins may have a low population or sensitivity of receptor sites for this peptide. However, this does not exclude the possibility that AVP could importantly affect vascular tone if this peptide would facilitate sympathetic neurotransmission or sensitize the vascular smooth muscle to the effects of norepinephrine. This might have important implications in our understanding of the detrimental effects associated with acute ischemic syndromes after autologous grafts in the arterial circulation or coronary bypass surgery.[22–24] Accordingly, the objective of this investigation was to determine whether low concentrations of AVP could modify the constrictor responses to adrenergic stimulation of

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human saphenous veins. We also determined whether the modulating effect of AVP on vascular responsiveness depends on activation of V_1 or V_2 receptors.

Methods

Vein segments were taken from portions of human saphenous veins of patients undergoing coronary artery bypass surgery (32 patients; 23 men and 9 women; age range, 52 to 71 years). The study was approved by the ethical committee of our institution, and informed consent was obtained from each patient before the study. During surgical preparation of the saphenous vein, the dilation procedure was avoided. The veins were immediately placed in chilled Krebs-Henseleit solution, and rings 3 mm long were cut for isometric recording of tension.

Two stainless steel L-shaped pins 200 μm in diameter were introduced through the lumen of the vein ring. One pin was fixed to the wall of the organ bath, and the other was connected to a force-displacement transducer (Grass FT03). Changes in isometric force were recorded on a Grass polygraph (model 7). Each vein ring was set up in a 4-mL bath that contained modified Krebs-Henseleit solution of the following millimolar composition: NaCl 115, KCl 4.6, $MgCl_2 \cdot 6H_2O$ 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25, glucose 11.1, and disodium EDTA 0.01. The solution was equilibrated with 95% oxygen and 5% carbon dioxide to a pH of 7.3 to 7.4. Temperature was held at 37°C. To establish the resting tension for maximal force development, a series of preliminary experiments was performed on vein rings of similar length and outer diameter that were exposed repeatedly to 100 mmol/L KCl. Basal tension was increased gradually until contractions were maximal. The optimal resting tension was 3 g. The vein rings were allowed to attain a steady level of tension during a 2- to 3-hour accommodation period before testing. Functional integrity of the endothelium was confirmed routinely at the beginning of the experiment by the presence or absence of relaxation induced by acetylcholine (10^{-7} to 10^{-6} mol/L) or substance P (10^{-9} mol/L) during contraction obtained with norepinephrine (10^{-7} to 3×10^{-7} mol/L).

Electrical field stimulation was provided by a Grass S88 stimulator via two platinum electrodes positioned on each side and parallel to the axis of the vein ring. To assess the nature of the contractile responses and to avoid direct stimulation of the smooth muscle, frequency-response relationships were determined on a group of veins in the presence and absence of 10^{-6} mol/L tetrodotoxin following previously described procedures.[25] In summary, the protocol was designed to find the optimal stimulation parameters (15 V, 0.2-ms duration) causing a contractile response that was completely eliminated by 10^{-6} mol/L tetrodotoxin. Frequency-response relationships were determined with 15-second trains of pulses at 1, 2, and 4 Hz. A period of 10 minutes was allowed between stimulations. The preparations were allowed to equilibrate for at least 10 minutes before they were incubated with tetrodotoxin (10^{-6} mol/L) or prazosin (10^{-6} mol/L). After 10 to 15 minutes of incubation with the antagonist, a second set of stimulations was performed. In each experiment, a second frequency-response relationship in untreated vein rings was run in parallel.

To study the effects of AVP on electrical field stimulation–induced responses, frequency-response relationships were determined in a separate group of experiments. After an initial set of stimulations, the vein rings were consecutively incubated with increasing concentrations of AVP (10^{-10} to 3×10^{-9} mol/L) for 10 minutes before another set of stimulations was given. As a control, four consecutive sets of stimulations were given to a group of untreated vein rings at identical intervals. Less than 10% variability in the magnitude of electrical field stimulation–induced contractions was observed for a given ring during four consecutive sets of control stimulations.

In another series of experiments, after a first frequency-response relationship was obtained, the preparations were incubated with either the V_1 receptor antagonist d(CH$_2$)$_5$Tyr(Me)AVP (10^{-6} mol/L), the V_1 receptor antagonist (10^{-8} to 10^{-6} mol/L) plus AVP (3×10^{-9} mol/L), the selective V_1 receptor agonist [Phe,^{2} Orn^8]-vasotocin (10^{-10} to 3×10^{-9} mol/L), the V_1 receptor antagonist (10^{-6} mol/L) plus the V_1 receptor agonist (3×10^{-9} mol/L), the V_2 vasopressin agonist desmopressin (10^{-9} to 10^{-7} mol/L), the V_2 receptor antagonist [d(CH$_2$)$_5$,

D-Ile,^{2} Ile,^{4} Arg^8]-vasopressin (10^{-8} to 10^{-6} mol/L) plus AVP (3×10^{-9} mol/L), or the reuptake blocker cocaine (10^{-6} mol/L) plus AVP (3×10^{-9} mol/L). After 10 to 15 minutes of incubation with the corresponding drug, a second set of stimulations was then performed. In each group of experiments, stimulations without any treatment were run in parallel.

Concentration-response curves for norepinephrine (10^{-9} to 3×10^{-5} mol/L) and KCl (5 to 120 mmol/L) were determined in a cumulative manner. Control (in the absence of AVP) and experimental (in the presence of AVP) data were obtained from separate vascular preparations. Another group of vein rings was incubated with the V_1 receptor antagonist (10^{-6} mol/L) plus AVP (3×10^{-9} mol/L) before exposure to norepinephrine or KCl.

In another group of experiments, electrical field stimulation was carried out under control conditions followed by a second set of stimulations in the presence of nifedipine (10^{-6} mol/L); then a third set of stimulations was performed in the presence of nifedipine plus AVP (3×10^{-9} mol/L). Frequency-response curves without any treatment were run in parallel. In another group of veins, norepinephrine (10^{-9} to 3×10^{-5} mol/L) was applied in the presence of either nifedipine (10^{-6} mol/L) or nifedipine plus AVP (3×10^{-9} mol/L), and the data were compared with those obtained from untreated (control) segments.

Drugs

The following drugs were used: tetrodotoxin, nifedipine, prazosin, norepinephrine hydrochloride, acetylcholine chloride, AVP acetate salt, [(1-(β-mercapto-β,β-cyclopentamethylenepropionic acid)-2-(O-methyl)-tyrosine, 8-arginine) vasopressin] [d(CH$_2$)$_5$Tyr(Me)AVP], deamino-8-D-arginine vasopressin (desmopressin), substance P acetate salt (Sigma Chemical Co), [Phe,^{2} Orn^8]-vasotocin, [d(CH$_2$)$_5$, D-Ile,^{2} Ile,^{4} Arg^8]-vasopressin (Peninsula Laboratories Europe), and cocaine chlorhydrate (Abelló). All drugs were dissolved in Krebs-Henseleit solution except nifedipine, which was dissolved initially in ethanol and further diluted in Krebs solution to the proper final concentration. Drugs were added to the organ bath in volumes of <70 μL. Stock solutions of the drugs were freshly prepared every day and kept on ice throughout the experiment.

Data Analysis

All values are expressed as mean±SE. Contractions are reported in absolute tension (grams) or as a percentage of response to KCl (100 mmol/L). EC_{50} values (concentrations of agonist producing half-maximal contraction) were determined from individual concentration-response curves by nonlinear regression analysis, and from these values the geometric means were calculated. The EC_{50} values were compared by an unpaired t test and an ANOVA with Scheffé's test as post hoc test. The number of rings taken from each patient varied from 8 to 16. Concentration-response curves of the tested agonists or frequency-response relationships were performed in the presence and absence of either AVP or the antagonists in rings obtained from the same patient; the responses obtained in each patient were averaged to yield a single value. Therefore, all number (n) values are presented as the number of patients from whom the blood vessel were obtained. For electrical stimulation experiments in which the same veins were stimulated in the absence and presence of AVP, a paired t test was used. Statistical significance was accepted at $P<.05$.

Results

Effects of AVP

AVP (10^{-9} to 10^{-6} mol/L) caused concentration-dependent contractions with an EC_{50} of 1.5×10^{-8} mol/L, which is similar to values previously reported by us.[21] The presence of the V_1 antagonist d(CH$_2$)$_5$Tyr(Me)AVP in the organ bath displaced the control curve to AVP to the right in a parallel manner (EC_{50}, 2.8×10^{-7} mol/L), but differences in the maximal tensions developed were not significant (23.1±3.3%, n=8, versus 23.3±3.8%, n=5, of response to 100 mmol/L KCl).
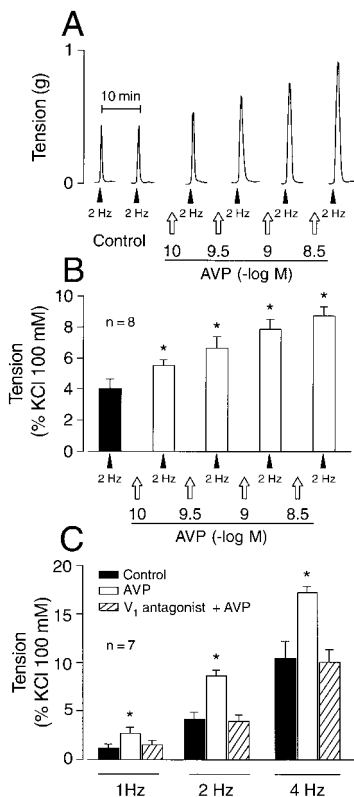
Figure 1. A, Tracings of contractile responses to field electrical stimulation (2 Hz) of isolated human saphenous veins under control conditions and after incubation with various concentrations of arginine vasopressin (AVP; 10^{-10} to 3×10^{-9} mol/L). B, Average contractions to electrical field stimulation in the absence and in the presence of increasing concentrations of AVP (10^{-10} to 3×10^{-9} mol/L). C, Effects of 3×10^{-9} mol/L AVP on frequency-dependent contractile responses to electrical field stimulation in the absence and in the presence of V_1 receptor antagonist d(CH$_2$)$_5$Tyr(Me)AVP (10^{-6} mol/L). *Significant differences from control value, $P < .05$.

The α_1-adrenoceptor blocker prazosin (10^{-6} mol/L) did not affect the concentration-response curve to AVP (EC$_{50}$, 1.1×10^{-8} mol/L; maximal response, $22.4 \pm 3.1\%$ of KCl contraction).

Effects of Electrical Stimulation

Electrical stimulation induced frequency-dependent increases in tension in all the experiments that were abolished by tetrodotoxin (10^{-6} mol/L) and prazosin (10^{-6} mol/L), thus indicating that the effect was due to the release of norepinephrine from perivascular adrenergic nerves acting on α_1-adrenoceptors.

AVP (10^{-11} to 3×10^{-11} mol/L) did not change the contractions to electrical stimulation at the frequencies used (1, 2, and 4 Hz). At higher concentrations (10^{-10} to 3×10^{-9} mol/L), AVP caused potentiation of the electrically evoked responses (Fig 1A and 1B). The V_1 receptor antagonist d(CH$_2$)$_5$Tyr(Me)AVP (10^{-6} mol/L) did not change control responses to electrical field stimulation but prevented the amplifying effect of AVP at all the frequencies used (Fig 1C).

The selective V_1 receptor agonist [Phe^2, Orn^8]-vasotocin induced a potentiation of electrical stimulation–evoked responses of a magnitude similar to that observed in the presence
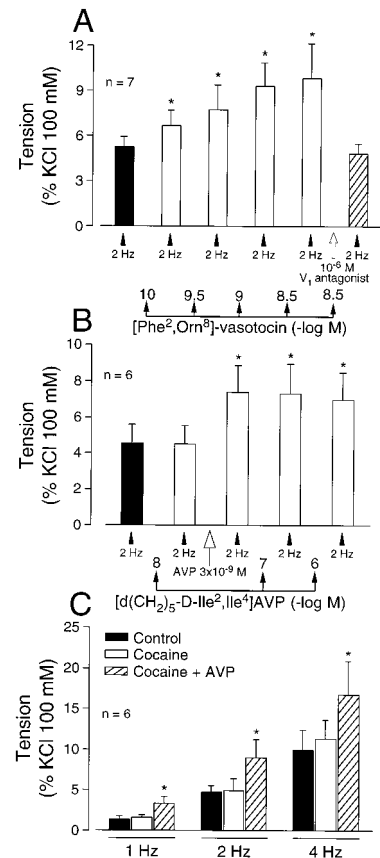

Figure 2. A, Contractile response to electrical field stimulation (2 Hz) in the absence and in the presence of increasing concentrations of the V_1 receptor agonist [Phe,^{2} Orn^8]-vasotocin (10^{-10} to 3×10^{-9} mol/L). The presence of the V_1 receptor antagonist d(CH$_2$)$_5$Tyr(Me)AVP (10^{-6} mol/L) abolished the augmentation of the contraction to electrical field stimulation by the V_1 receptor agonist. B, Contractile responses to electrical field stimulation in the absence and in the presence of increasing concentrations of the V_2 receptor antagonist [d(CH$_2$)$_5$, D-Ile,^{2} Ile,^{4} Arg^8]-vasopressin (10^{-8} to 10^{-6} mol/L). The potentiation induced by AVP (3×10^{-9} mol/L) was not affected in the presence of the V_2 receptor antagonist. C, Frequency-response relationship in the absence and presence of cocaine (10^{-6} mol/L) or cocaine together with AVP (3×10^{-9} mol/L). Values are mean$\pm$SEM. *Significant differences ($P < .05$) from control value.

of AVP. This potentiation was also inhibited in the presence of the V_1 receptor antagonist d(CH$_2$)$_5$Tyr(Me)AVP (10^{-6} mol/L) (Fig 2A).

To determine whether V_2 receptors are involved in the effects of AVP on field electrical stimulation, frequency-response relationships were obtained in the absence and in the presence of the V_2 receptor antagonist [d(CH$_2$)$_5$, D-Ile^2, Ile^4, Arg^8]-vasopressin. Fig 2B shows that the potentiation induced by AVP was not modified in the presence of 10^{-8} to 10^{-6} mol/L of the V_2 receptor antagonist. In addition, the selective V_2 receptor agonist desmopressin (10^{-9} to 10^{-7} mol/L) did not modify the control frequency-response relationship ($P > .05$, n=6) (results not shown).

Blockade of neuronal catecholamines reuptake by cocaine (10^{-6} mol/L) had no effect on the potentiating effects of AVP on electrical field stimulation (Fig 2C).
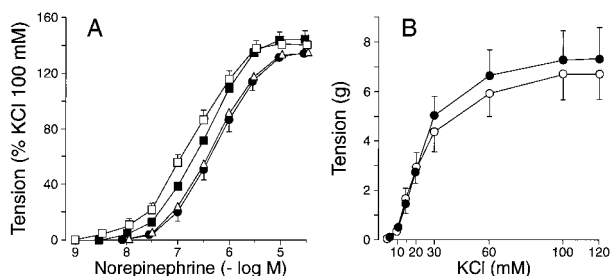
Figure 3. A, Contractile effects of norepinephrine in the absence (●, n=6) and in the presence of arginine vasopressin (AVP) (■, 10^{-9} mol/L, n=4; □, 3×10^{-9} mol/L, n=4) and in the presence of the V₁ receptor antagonist (10^{-6} mol/L) together with AVP (3×10^{-9} mol/L, △, n=4). B, Concentration-response curves to KCl in the absence (●, n=9) and in the presence (○, n=7) of 3×10^{-9} mol/L AVP. Values are mean±SEM.

Effect of AVP on Norepinephrine- and KCl-Induced Contraction

AVP potentiated norepinephrine-induced contractions in a concentration-dependent manner (Fig 3A). The norepinephrine EC_{50} values and maximal responses in the presence and absence of AVP are shown in the Table. The V₁ receptor antagonist d(CH₂)₅Tyr(Me)AVP produced a parallel, rightward shift of the potentiating effects of 3×10^{-9} mol/L AVP on the norepinephrine concentration-response curve. At 10^{-6} mol/L, the V₁ inhibitor brought the EC_{50} to values similar to those obtained in the norepinephrine control curve. In contrast, AVP (10^{-10} to 3×10^{-9} mol/L) did not affect the concentration-response curve to KCl (10 to 120 mmol/L) (Fig 3B).

AVP and Calcium

The dihydropyridine calcium antagonist nifedipine (10^{-6} mol/L) did not significantly change the contraction induced by AVP and electrical field stimulation (Fig 4A and 4B). The presence of nifedipine diminished maximal responses to norepinephrine, but EC_{50} was not altered (6.6×10^{-7} versus 5.2×10^{-7} mol/L) (Fig 4C). In addition, the enhancement of
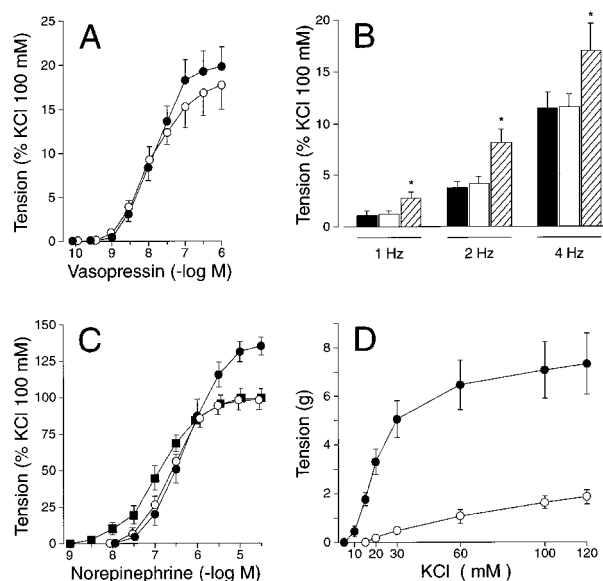

Figure 4. A, Concentration-response curves to AVP in the absence (●, n=7) and in the presence (○, n=6) of nifedipine (10^{-6} mol/L). B, Frequency-response relationship under control conditions (solid bars, n=5) and in the presence of nifedipine (10^{-6} mol/L, open bars, n=5) or nifedipine plus AVP (3×10^{-9} mol/L, hatched bars, n=5). C, Concentration-response curves to norepinephrine in the absence (●, n=6) and in the presence of either nifedipine (10^{-6} mol/L, ○, n=8) or nifedipine together with AVP (3×10^{-9} mol/L, ■, n=6). D, Concentration-response curves to KCl in the absence (●, n=7) and in the presence of nifedipine (10^{-6} mol/L, ○, n=7). Values are mean±SEM. *Significant differences from control values, $P<.05$.

the contractile responses to electrical field stimulation and norepinephrine by AVP was identical to that observed in the absence of nifedipine (Fig 4B and 4C). However, KCl-induced contractions were significantly reduced in the presence of nifedipine (10^{-6} mol/L) (Fig 4D).

Discussion

The results of this study demonstrate that in the human saphenous vein, low concentrations of AVP enhance the

EC_{50} Values and Maximal Contractions to Norepinephrine Alone (Control) and in the Presence of Either AVP or the V₁ Receptor Antagonist Together With AVP

Norepinephrine	EC_{50}, mol/L (95% Confidence Interval)	Maximal Responses, %±SEM
Control (n=6)	6.87×10^{-7}	135.2 ± 6.1
	$(6.65\times10^{-7}-7.09\times10^{-7})$	
With AVP		
3×10^{-10} mol/L (n=4)	2.79×10^{-7}*	126.9 ± 9.1
	$(2.62\times10^{-7}-2.96\times10^{-7})$	
10^{-9} mol/L (n=4)	2.64×10^{-7}*	152.9 ± 4.1
	$(1.18\times10^{-7}-4.1\times10^{-7})$	
3×10^{-9} mol/L (n=4)	1.04×10^{-7}*	140.3 ± 7.9
	$(0.53\times10^{-7}-1.47\times10^{-7})$	
With V₁ receptor antagonist	6.08×10^{-7}	133.9 ± 6.2
(10^{-6} mol/L)+AVP (3×10^{-9} mol/L) (n=4)	$(5.81\times10^{-7}-6.19\times10^{-7})$	

AVP indicates arginine vasopressin. Values are mean±SEM. Maximal contraction is expressed as a percentage of response to 100 mmol/L KCl.

*$P<.05$ vs control rings.

contractile effects of electrical field stimulation and norepinephrine. The potentiating effects occur at AVP concentrations substantially lower than those required to produce a clear direct contractile response. In a previous work,[21] we found that contractions of human saphenous veins in response to AVP are relatively low compared with human arteries, indicating that these veins may have a low population or sensitivity of receptor sites for this peptide. However, an interesting finding of the present study is that the low responsiveness of the saphenous vein coincides with a high sensitivity to the modulating effects of AVP on adrenergic-mediated responses. Thus, it appears that the indirect (potentiating) effects of AVP on human saphenous vein may act synergistically with the effects of adrenergic stimulation.

Previous studies have suggested the existence of V_2 receptors in some vascular beds that could mediate vasodilatation. Administration of either V_2 receptor agonists or vasopressin during V_1 receptor blockade increased blood flow in some vascular beds and decreased peripheral resistance in both humans and dogs.[11–13] In the human saphenous vein, both AVP and the V_2 receptor agonist desmopressin cause relaxation that seems largely dependent on the release of dilating prostaglandins.[21] Therefore, we examined the potential role of V_2 receptor stimulation in the enhancing effects of AVP. The results do not support the intervention of V_2 receptors in these responses. First, the selective V_2 receptor agonist desmopressin did not modify responses to electrical field stimulation. On the other hand, the V_2 receptor antagonist [d(CH$_2$)$_5$, D-Ile,^{2} Ile,^{4} Arg^8]-vasopressin did not affect the potentiation induced by AVP. In contrast, the selective V_1 receptor antagonist d(CH$_2$)$_5$Tyr(Me)AVP inhibited the amplifying effects of AVP on electrical field stimulation and norepinephrine-induced contractions in a concentration-dependent manner. In addition, the selective V_1 receptor agonist [Phe,^{2} Orn^8]-vasotocin induced potentiating effects similar to those observed in the presence of AVP. Therefore, the results exclude a role for V_2 receptors in the potentiating effects of AVP and are consistent with the hypothesis that V_1 receptor stimulation in the absence of direct contraction is followed by enhancement of responses to both endogenous and exogenous norepinephrine.

It might be conceived that the effects of AVP on electrical field stimulation contractions could involve an effect on adrenergic nerves, leading to release of norepinephrine, or alternatively AVP could act with norepinephrine at postjunctional receptor sites. Because norepinephrine release was not measured in this study, a contribution of presynaptic facilitating effects cannot be excluded. The fact that the concentration-response curve to AVP was not modified by prazosin, an α_1-adrenoceptor blocker, suggests that the action of this peptide does not involve release of norepinephrine. The possibility that AVP could block the reuptake of norepinephrine and therefore enhance the contractile responses is unlikely because the potentiating effects were still evident in the presence of cocaine. Alternatively, AVP-induced potentiation could be due to alterations at the receptor level, leading to an increased affinity of norepinephrine for its receptor. This may be a likely explanation because AVP increased the contractions to exogenously applied norepinephrine. Thus, our data are consistent with the suggestion that potentiation of the effects of

nerve stimulation by AVP corresponds to a postsynaptic enhancement of the action of norepinephrine.

We also considered the possibility that stimulation of V_1 receptors may facilitate calcium entry through dihydropyridine calcium channels. Our results show that nifedipine did not affect the direct contractions of AVP or prevent the potentiating action of AVP on norepinephrine- and electrical field stimulation–induced contractions. This indicates that influx of extracellular calcium through dihydropyridine-sensitive calcium channels does not importantly contribute to the direct contractile effects of AVP or participate in the potentiating effect of AVP on adrenergic contractions. In line with that interpretation, our results show that AVP did not affect the concentration-response curve to KCl, an agent that induces contraction by facilitating calcium entry through voltage-dependent calcium channels. Other mechanisms of calcium handling such as an increase in inositol phosphate metabolism and/or increase calcium release from intracellular reservoirs[1,26,27] may be involved in the potentiating effects of AVP. In contrast, in human mesenteric arteries, AVP brings about a facilitation of extracellular Ca^{2+} entry by KCl through voltage-dependent calcium channels.[20] The precise explanation for such tissue specificity is not known, but it may be due to differences in distribution and pharmacological properties of V_1 vascular receptors between mesenteric arteries and saphenous veins.

In contrast to the present results, Hilgers et al[18] did not find any effect of AVP on sympathetic transmission in an in vitro perfused rat hind limb preparation. A common finding in the vascular effects of this peptide is the heterogeneity of responsiveness depending on regional and species differences[28,29] and may be due to different populations or sensitivity of receptor sites for AVP.[6,8,30] In addition, Hilgers et al[18] used only one concentration of AVP (0.3 nmol/L), which probably was insufficient to modulate neurogenic responses. Because the present findings show that the potentiating effects of AVP are concentration dependent, it is conceivable that differences between the concentrations of AVP used may also account for the discrepant findings of our study and those of Hilgers et al.[18]

Some of the present observations may be of clinical significance. Several reports indicate that large arteries and veins from various animal species may synthesize and store an AVP immunoreactive material that appears identical to authentic AVP, thus suggesting that the vascular peptide is of local rather than neurohypophysial origin.[31,32] This raises the possibility that locally released AVP may reach concentrations high enough to act synergistically with the adrenergic neurotransmitter. The concentration of AVP in this study may be lower than those expected to occur in response to hypotension, dehydration, and exercise and in some patients with hypertension or congestive heart failure.[33–35] Consequently, the amplifying effect of AVP on adrenergic-mediated constriction, shown in the present experiments, may importantly contribute to vascular mechanisms involved in acute ischemic syndromes associated with venous grafts. The human saphenous vein can undergo spasm, which is a clinically relevant problem, immediately after autologous grafts in the arterial circulation or coronary bypass surgery.[22–24] In view of the specificity and potency of the V_1 antagonist d(CH$_2$)$_5$Tyr(Me)AVP, it seems

appropriate to consider the use of V_1 receptor antagonists in circumstances in which AVP plasma concentrations are raised. Furthermore, provided that V_1 receptor blockade is present, AVP induces marked dilatation of previously contracted human arteries[5] and saphenous veins,[21] probably because of the release of vasodilatory prostaglandins from the vessel wall. These findings could explain the reduction of vascular resistance that has been observed after intravenous administration of the V_1 antagonist d(CH$_2$)$_5$Tyr(Me)AVP in patients with hypertension or congestive heart failure in the presence of high plasma AVP levels.[34,36]

In conclusion, the results of the present study demonstrate that AVP, in addition to its direct vasoconstrictor effect, strongly potentiates the contractions of human saphenous veins to norepinephrine and stimulation of perivascular sympathetic nerves. Both the direct and indirect effects of AVP appear to be mediated by V_1 receptor stimulation. The potentiation induced by AVP is not related to activation of dihydropyridine-sensitive calcium channels.

Acknowledgments

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