Endothelium-dependent relaxation of human saphenous veins in response to vasopressin and desmopressin

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Purpose: The goal of this study was to determine the effects of vasopressin and the selective V_2-receptor agonist desmopressin on human saphenous veins, with special emphasis on endothelium-mediated responses.

Methods: Human saphenous vein segments were obtained from 35 patients undergoing coronary bypass surgery. Paired segments, one normal and the other deendothelized by gentle rubbing, were mounted for isometric recording of tension in organ baths. Concentration-response curves to vasopressin and desmopressin were determined in the presence and in the absence of either the V_1-receptor antagonist d(CH_2)$_5$Tyr(Me)AVP (10^{-6} mol/L), the V_1-V_2-receptor antagonist desGly-d(CH_2)$_5$D-Tyr(Et)ValAVP (10^{-6} mol/L), indomethacin (10^{-6} mol/L), or N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME, 10^{-4} mol/L).

Results: In vein rings under resting tension, vasopressin produced concentration-dependent, endothelium-independent contractions with a concentration of vasopressin producing half-maximal contractions (EC_{50}) of 3.44×10^{-8} mol/L. The vasopressin V_1-receptor antagonist (10^{-6} mol/L) displaced the control curve to vasopressin 9.86-fold to the right in a parallel manner. In precontracted vein rings previously treated with the V_1-antagonist (10^{-6} mol/L), vasopressin caused endothelium-dependent relaxations. This relaxation was reduced significantly by indomethacin (10^{-6} mol/L) and unaffected by the V_1-V_2-receptor antagonist (10^{-6} mol/L) or by L-NAME (10^{-4} mol/L). Desmopressin caused endothelium-dependent relaxations in precontracted vein rings that were inhibited by the mixed V_1-V_2-receptor antagonist and by indomethacin, but not by the V_1-antagonist or by pretreatment with L-NAME.

Conclusions: These observations indicate that vasopressin exerts contractile effects on human saphenous vein by V_1-receptor stimulation. Vasopressin causes dilatation of human saphenous vein only if V_1-receptor blockade is present. This relaxation appears to be mediated by the release of relaxant prostaglandins, probably derived from endothelial cells, and is independent of V_2-receptor stimulation or release of nitric oxide. Desmopressin elicits relaxation that is largely dependent on V_2-receptor stimulation, which may bring about the release of dilating prostaglandins from the endothelial cells. (J Vasc Surg 1997;25:696-703.)

Vasopressin causes powerful constriction in a variety of vascular regions.[1-3] The vasopressin receptor designated V_1 seems to mediate the vasoconstrictor action of the peptide, whereas its antidiuretic action is mediated through V_2, cyclic adenosine monophosphate–dependent receptors.[4-6] With regard to human vessels, vasopressin causes V_1-mediated constriction in isolated mesenteric arteries[7,8] and in submucosal arterioles of the intestinal microcirculation.[9] Further studies of the physiologic effects of vasopressin have suggested the existence of V_2-receptors in some vascular beds that could mediate vasodilatation. Administration of either V_2-agonists or vasopressin during V_1-receptor blockade increased blood flow in some vascular beds and decreased peripheral vascular resistance in both humans and dogs.[10-12]

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Supported by the Comisión Interministerial de Ciencia y Tecnología, Ministerio de Sanidad and Generalitat Valenciana.

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0741-5214/97/$5.00 + 0 24/1/77413

Recent experiments suggest that the vasopressin-induced vasodilatation in the human forearm is caused by release of nitric oxide mediated by V_2-receptor stimulation,[13] whereas in human isolated mesenteric and cerebral arteries the vasodilatation seems to be the result of release of dilating prostaglandins from the vessel wall.[8,14]

To date, no information is available concerning the effects and pharmacologic receptors of vasopressin and desmopressin in human saphenous veins. The effects of vasopressin in this vascular bed may be of physiologic and pathologic significance in those states characterized by an increased plasma vasopressin level, such as dehydration and exercise, as well as in some patients with hypertension or congestive heart failure.[15-17] Moreover, the endothelial capacity for nitric oxide and prostacyclin production in response to vasopressin may have important implications in understanding the pathophysiology of veins used as autologous grafts in the arterial circulation or in coronary artery bypass surgery. Accordingly, the objective of this investigation was to determine the effects of vasopressin and desmopressin in human saphenous veins. Observations were made in the presence and absence of endothelium, as well as with vasopressin receptor antagonists and inhibitors of cyclooxygenase.

METHODS

Vein segments were taken from portions of human saphenous veins of patients undergoing coronary artery bypass surgery for coronary artery disease (35 patients [29 men and six women; age range, 37 to 76 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. The outside diameter of the rings was measured with an ocular micrometer within a Wild M8 zoom microscope (Heerbrugg, Switzerland) and ranged from 3.2 to 4 mm. In approximately 50% of the vein rings, the endothelium was removed mechanically by insertion of a roughened stainless steel wire into the lumen and gently rolling the rings on wet filter paper.

Two stainless steel 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: sodium chloride, 115; potassium chloride, 4.6; magnesium chloride, 1.2; calcium chloride, 2.5; sodium bicarbonate, 25; glucose, 5; and disodium ethylenediaminetetraacetic acid, 0.01. The solution was equilibrated with 95% oxygen and 5% carbon dioxide to give 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 were performed on rubbed and unrubbed vein rings of similar length and outer diameter that were exposed repeatedly to 60 mmol/L potassium chloride. Basal tension was increased gradually until contractions were maximal. The optimal rest tension was 3 gm. The vein rings were allowed to attain a steady level of tension during a 2-hour accommodation period before testing. The contractile response to 60 mmol/L potassium chloride was similar in rubbed and unrubbed vein rings (5845 ± 765 versus 6258 ± 480 mg; $p > 0.05$). To study relaxation, vein rings were precontracted with 10^{-7} to 3×10^{-7} mol/L norepinephrine, which gave a contraction ranging from 50% to 70% of contractions produced by 60 mmol/L potassium chloride.

Functional integrity of the endothelium was confirmed routinely 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). After each experiment the vein rings were carefully opened flat and stained with silver nitrate to visualize the endothelium. Only results from rings with more than 70% of the endothelium were considered to be control rings. Vessels in which the endothelium had been rubbed never showed more than 5% of their intima covered with endothelium.

After the equilibration period, concentration-response curves for vasopressin (10^{-9} to 10^{-6} mol/L) were obtained in paired rings under resting tension in the absence and presence of the V_1-antagonist $d(CH_2)_5Tyr(Me)AVP$ (10^{-6} mol/L). To check the possibility that the V_2-receptor agonist desmopressin is an antagonist of the V_1-receptor–mediated contraction, the effects of vasopressin were evaluated in the presence of 10^{-7} mol/L desmopressin.

To study vasopressin-induced relaxation, rings were incubated with the V_1-receptor antagonist $d(CH_2)_5Tyr(Me)AVP$ (10^{-6} mol/L) and then contracted with 10^{-7} to 3×10^{-7} mol/L norepineph-

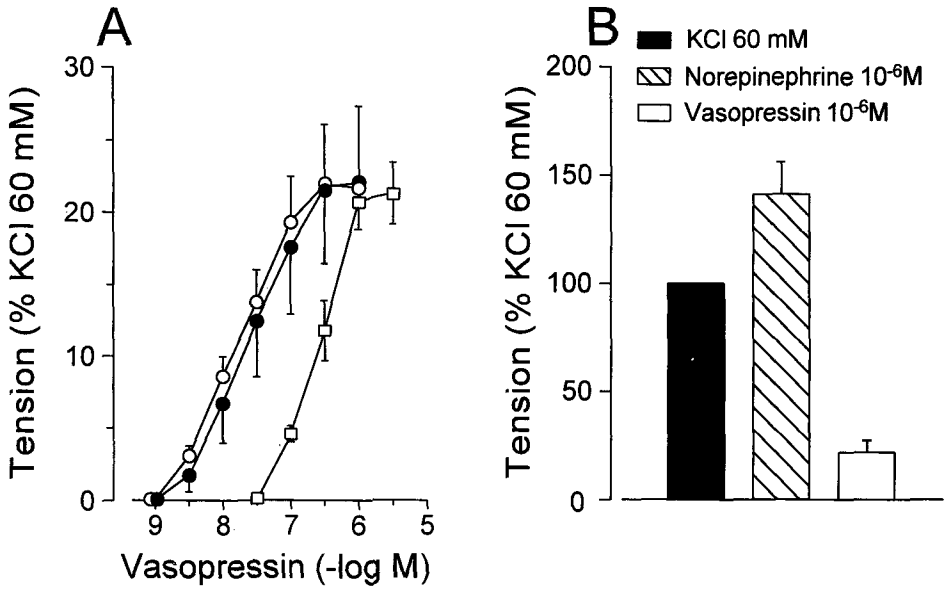

Fig. 1. A, Concentration-response curves for vasopressin determined in human saphenous vein rings with (*solid circles;* n = 8) and without(*open circles;* n = 6) endothelium and in the presence of the V_1-antagonist $d(CH_2)_5Tyr(Me)AVP$ in rings with endothelium (*open squares;* 10^{-6} mol/L; n = 6). **B,** Contractile effects of potassium chloride (*KCl,* 60 mmol/L; n = 10), norepinephrine (10^{-6} mol/L; n = 6), and vasopressin (10^{-6} mol/L; n = 8). Results are expressed as a percentage of the contraction developed by 60 mmol/L potassium chloride by each preparation. Values are means ± SEM.

rine. After a stable contraction was obtained, concentration-response curves to vasopressin (10^{-11} to 3×10^{-7} mol/L) were determined in paired rings in the absence and presence of either the V_1-V_2–receptor antagonist desGly-$d(CH_2)_5$D-Tyr(Et)ValAVP (10^{-6} mol/L), indomethacin (10^{-6} mol/L), or N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME; 10^{-4} mol/L). Concentration-response curves to the V_2-agonist desmopressin (10^{-11} to 3×10^{-7} mol/L) were also determined from a group of precontracted rings in the absence and in the presence of either the mixed V_1-V_2–antagonist (10^{-6} mol/L) or indomethacin (10^{-6} mol/L). As a control for each experimental group, vein rings were contracted in a way similar to that described above and left untreated (without desmopressin or vasopressin addition to the bath). In these vein rings, less than 10% variability in tension below or above the elevated tension was observed throughout the experiment.

Antagonists were added to the organ bath chambers 15 minutes before the initiation of cumulative concentration-response curves to agonists. Only one concentration-response curve to vasopressin or desmopressin was made in each vein ring.

Drugs. The following drugs were used: norepinephrine hydrochloride, acetylcholine chloride, L-NAME, arginine vasopressin acetate salt, deamino-Cys D-arginine vasopressin acetate salt (desmopressin), $d(CH_2)_5Tyr(Me)AVP$ [(1-(β-mercapto-β,β-cyclopentamethylenepropionic acid) 2-(*O*-methyl)-tyrosine, 8-arginine) vasopressin], desGly-$d(CH_2)_5$D-Tyr(Et)ValAVP [(1-(β-mercapto-β,β-cyclopentamethyleneпropionic acid) 2-(*O*-ethyl)-D-tyrosine, 4-valine, 8-arginine, 9-desglycine) vasopressin], substance P acetate salt and sodium nitroprusside dihydrate (Sigma Chemical Co., St. Louis, Mo.).

Drugs were prepared and diluted in distilled water, except for indomethacin. Indomethacin was dissolved in absolute ethanol and sodium bicarbonate solution (150 mmol/L) and readjusted to a pH of 7.4 with hydrochloric acid before use. Fresh stock solutions of the drugs were prepared every day.

Data analysis. Values for concentrations of vasopressin producing half-maximal contractions (EC_{50}) were determined from individual concentration-response curves by nonlinear regression analysis; the geometric means were calculated from these values. Relaxation was expressed as a percentage of the norepinephrine-induced contraction. All values are expressed as mean ± SEM. In each experimental group, n indicates the number of patients. At least eight vein rings were obtained

from each patient. Differences between agonist- and antagonist-treated groups were assessed by one-way analysis of variance. Differences between means were identified by *t* test. Statistical significance was accepted at $p < 0.05$.

RESULTS

Effects of vasopressin in vein rings under resting tension. Vasopressin (10^{-9} to 10^{-6} mol/L) caused concentration-dependent contractions, with an EC_{50} of 3.44×10^{-8} mol/L. These contractions were endothelium-independent (Fig. 1, *A*). The maximum tensions developed were significantly less than those produced by potassium chloride (60 mmol/L) or norepinephrine (3×10^{-6} mol/L) in the same preparations (Fig. 1, *B*). EC_{50} values for vasopressin in saphenous veins are of a magnitude greater than those obtained in human arteries from different vascular beds (7.2×10^{-10} mol/L and 5.9×10^{-10} mol/L for human cerebral and mesenteric arteries respectively).[8,14] The concentration-response curves to vasopressin were of the same magnitude in veins with or without endothelium (Fig. 1, *A*). The presence of the V_1-antagonist $d(CH_2)_5Tyr(Me)AVP$ (10^{-6} mol/L) in the organ bath displaced the control curve for vasopressin 9.86-fold ($p < 0.05$) to the right in a parallel manner (EC_{50}, 3.39×10^{-7} mol/L), but differences in the maximal tensions developed were not significant ($p > 0.05$).

Effects of vasopressin in precontracted rings. To determine whether vasopressin induces relaxation in precontracted veins, increasing concentrations of this peptide were added to rings during submaximal contraction induced by norepinephrine (10^{-7} to 3×10^{-7} mol/L). Fig. 2 shows that vasopressin caused further contractions in precontracted arteries with and without endothelium. In these rings the ability of the smooth muscle to relax was tested by adding 10^{-7} mol/L sodium nitroprusside when the maximal contractions had been attained with vasopressin. Under these conditions sodium nitroprusside caused almost complete relaxation of both normal and endothelium-denuded rings.

When the vein rings were pretreated with the V_1-receptor antagonist $d(CH_2)_5Tyr(Me)AVP$ (10^{-6} mol/L) to prevent vasopressin-induced constriction and when they were contracted with norepinephrine (10^{-7} to 3×10^{-7} mol/L), vasopressin (10^{-11} to 3×10^{-7} mol/L) produced concentration-dependent relaxations that were greater ($p < 0.05$) in veins with endothelium than in endothelium-denuded rings (Fig. 3, *A*). The mixed V_1-V_2–receptor antagonist $desGly\text{-}d(CH_2)_5D\text{-}Tyr(Et)ValAVP$ (10^{-6} mol/L) had no effect on vasopressin-induced relaxation (Fig. 3, *B*). However, the presence of indomethacin (10^{-6} mol/L) significantly ($p < 0.05$) reduced the relaxation induced by vasopressin (Fig. 3, *B*). On the other hand, L-NAME (10^{-4} mol/L) treatment had no effect on vasopressin-induced relaxation (Fig. 3, *B*). The same concentration of L-NAME abolished completely the relaxations to acetylcholine (10^{-7} to 10^{-6} mol/L) in vein rings with endothelium.

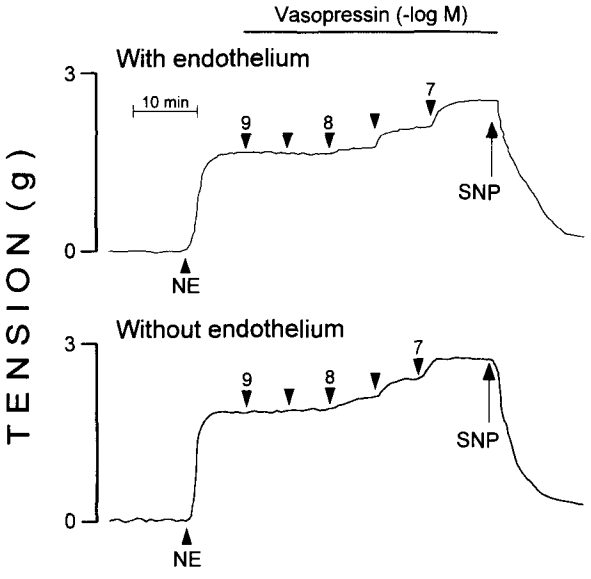

Fig. 2. Contractile effects of vasopressin in saphenous vein rings with and without endothelium previously contracted with norepinephrine (*NE*, 10^{-7} mol/L). Sodium nitroprusside (*SNP*, 10^{-5} mol/L) caused almost complete relaxation of vein rings.

Effects of desmopressin. The selective antidiuretic agonist desmopressin (10^{-11} to 3×10^{-7} mol/L) did not produce significant changes in the resting tension of saphenous veins with (n = 4) or without (n = 4) endothelium. In addition, the presence of desmopressin (10^{-7} mol/L) did not affect the concentration-response curve to vasopressin (results not shown). In veins contracted with norepinephrine (10^{-7} to 3×10^{-7} mol/L), desmopressin caused concentration-dependent relaxations that were greater ($p < 0.05$) in segments with endothelium than in endothelium-denuded rings (Fig. 4, *A*). The specific V_1-receptor antagonist $d(CH_2)_5Tyr(Me)AVP$ (10^{-6} mol/L) did not have a significant effect on desmopressin-induced relaxations (Fig. 4, *A*). In contrast, the V_1-V_2–receptor antagonist $desGly\text{-}d(CH_2)_5D\text{-}Tyr(Et)ValAVP$ (10^{-6} mol/L) signifi-

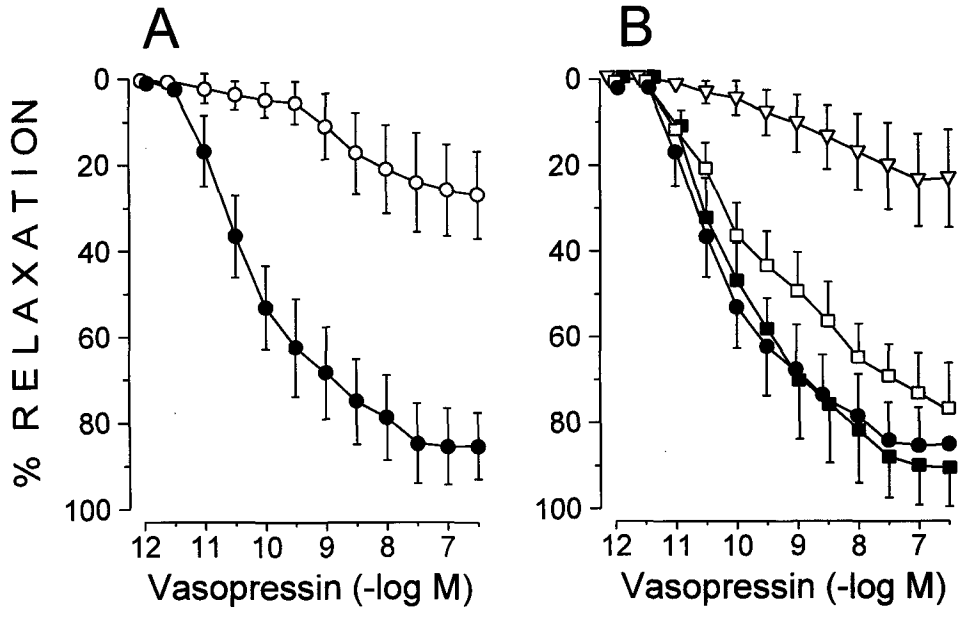

Fig. 3. Relaxation to vasopressin of vein rings previously treated with the antagonist $d(CH_2)_5Tyr(Me)AVP$ (10^{-6} mol/L) and contracted with norepinephrine (10^{-7} to 3×10^{-7} mol/L). **A,** Concentration-response curves in the presence (*solid circles;* n = 8) and absence (*open circles;* n = 8) of endothelium. **B,** Relaxation to vasopressin in rings with endothelium in the absence of indomethacin *(solid circles)* and presence of indomethacin (*open triangles;* 10^{-6} mol/L; n = 7) or N^G-nitro-L-arginine methyl ester hydrochloride (*open squares;* 10^{-4} mol/L; n = 6) and in the presence of the V_1-V_2–antagonist desGly-$d(CH_2)_5$D-Tyr(Et)ValAVP (*solid squares;* 10^{-6} mol/L; n = 4). Values are means ± SEM.

cantly reduced desmopressin-mediated relaxation ($p < 0.05$; Fig. 4, *A*). The presence of indomethacin (10^{-6} mol/L) but not L-NAME (10^{-4} mol/L) significantly ($p < 0.05$) reduced the relaxation induced by desmopressin (Fig. 4, *B*).

DISCUSSION

Our results show that vasopressin exerts relatively low contractile effects (compared with potassium chloride depolarization or α-adrenergic stimulation) on human saphenous veins. The low potency of vasopressin-expressed in terms of EC_{50} values-and the low magnitude of its maximal effects were features consistently observed in these experiments, indicating that, compared with human arteries, these veins may have a low population or sensitivity of receptor sites for this peptide.[8,14] The low responsiveness of saphenous veins to vasopressin does not reflect a nonspecific effect or an effect caused by the state of the preparation because considerably higher contractions were obtained with norepinephrine and potassium chloride. The V_1-antagonist $d(CH_2)_5Tyr(Me)AVP$ produced a 9.86-fold shift to the right of the control concentration-response curve to vasopressin, presumably because of an equilibrium competitive agonist-antagonist interaction. The same concentration of the antagonist produced a 1250- and 1525-fold shift in human cerebral and mesenteric arteries, respectively,[8,14] values greater than that obtained in the present study. It seems likely that the properties of the vasopressin receptor of human saphenous veins that determine the affinity for a common antagonist are lower than those of the corresponding receptors in human arteries.

Our data also show that the vasopressin-induced contraction is not linked to the presence of an intact endothelium, indicating that vasodilator substances secreted by endothelial cells under basal spontaneous conditions[18] do not counteract the contractile effects of vasopressin on smooth muscle cells. Maximal contractions to 60 mmol/L potassium chloride did not differ between rubbed and unrubbed veins, which suggests that a change in the mechanical properties of the vessel wall caused by endothelium removal does not play an important role on reactivity of rubbed veins. In agreement with the results of this study, previous experiments have shown that vasopressin causes endothelium-independent contrac-

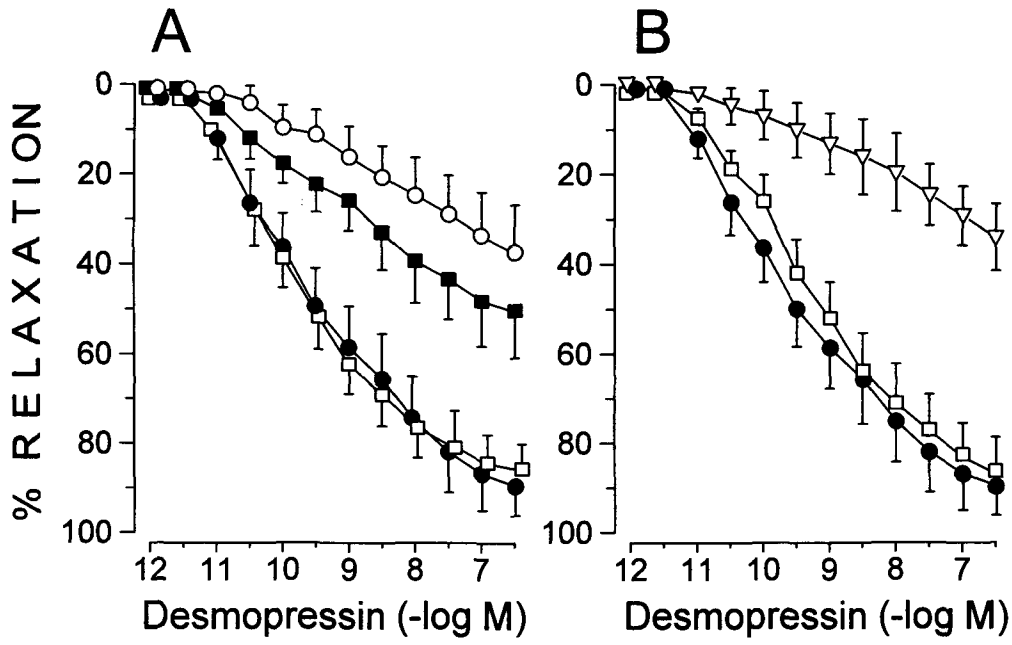

Fig. 4. Relaxation to desmopressin of vein rings precontracted with norepinephrine (10^{-7} to 3×10^{-7} mol/L). **A,** Responses to desmopressin in the presence *(solid circles;* n = 7) and absence *(open circles;* n = 6) of endothelium and in the presence of the V_1-V_2-antagonist desGly-d$(CH_2)_5$D-Tyr(Et)ValAVP *(solid squares;* 10^{-6} mol/L; n = 5) or V_1-antagonist d$(CH_2)_5$Tyr(Me)AVP *(open squares;* 10^{-6} mol/L; n = 4) in rings with endothelium. **B,** Responses to desmopressin in rings with endothelium in the absence of indomethacin *(solid circles;* n = 6) and presence of indomethacin *(open triangles;* 10^{-6} mol/L; n = 7) or N^G-nitro-L-arginine methyl ester hydrochloride *(open squares;* 10^{-4} mol/L; n = 6). Values are means ± SEM.

tions in human mesenteric,[8] cerebral,[19] and uterine[20] arteries. Therefore it is most likely that the contractile effects of vasopressin on human saphenous veins are caused by direct stimulation of specific receptors located on smooth muscle cells.

Studies in healthy subjects have shown that the effects of vasopressin on human forearm blood flow-as measured by venous occlusion plethysmography-are biphasic.[21,22] The lower doses of vasopressin (<0.1 ng/kg per minute) caused vasoconstriction, whereas the higher doses (>0.5 ng/kg per minute) caused vasodilation. In one study it was observed that vasopressin produced a decrease in digital blood flow together with forearm vasodilation.[12] In our experiments in human saphenous veins, we have observed only constriction in response to vasopressin, even when the arterial segments were precontracted with norepinephrine. Therefore it appears that, under the present in vitro conditions, V_1-mediated contraction is the predominant effect in response to vasopressin.

The results obtained in contracted veins show that vasopressin elicits concentration-dependent relaxation only if V_1-receptor blockade is present. In addition, these results show that desmopressin, a highly specific antidiuretic V_2-receptor agonist,[23] induced concentration-dependent relaxation similar to that observed in response to the combination of vasopressin plus the V_1-antagonist. In contrast to the results described here, no evidence for the presence of V_2-receptor–mediated dilatation was obtained after application of vasopressin or desmopressin to isolated submucosal arterioles of the intestinal circulation of guinea pigs, rabbits, and humans.[9] In addition to regional differences, it is possible that the size of the vessels used may be a factor in the response to desmopressin, as previously reported for vasopressin.[24,25]

Until now the possibility that vasopressin and desmopressin may dilate human veins through V_2-receptors has not been investigated. We used the mixed V_1-V_2-vasopressin antagonist desGly-d$(CH_2)_5$D-Tyr(Et)ValAVP because it appears to be the most potent in vitro antagonist of human vasopressin-stimulated renal adenylate cyclase.[26] It also antagonizes exogenous vasopressin-stimulated an-

tidiuresis in conscious water-loaded rats.[27] From a theoretical point of view, this analog would be a highly potent specific vascular V_2-antagonist. In the present experiments, the mixed V_1-V_2–antagonist desGly-d$(CH_2)_5$D-Tyr(Et)ValAVP prevented the relaxation induced by desmopressin, whereas the V_1-antagonist d$(CH_2)_5$Tyr(Me)AVP did not. These results suggest that the relaxation observed in response to desmopressin is endothelium-dependent and mediated by a receptor similar to the renal V_2-receptor, a finding similar to that previously reported in dogs[28,29] and in isolated human arteries.[8,14] In addition, treatment with indomethacin, but not L-NAME, inhibited the desmopressin-induced relaxation, suggesting that desmopressin stimulates the release of vasodilator prostaglandins from endothelial cells. Derkx et al.[30] reported that desmopressin caused a decrease in diastolic blood pressure and an increase in heart rate in healthy volunteers. They suggested that the vasodilating properties of desmopressin were caused by competitive antagonism of endogenous vasopressin on vascular V_1-receptors. However, similar hemodynamic effects of desmopressin administration have been described in patients with central diabetes insipidus, who lack endogenous vasopressin.[11,31] In the present experiments and in those of Johns[32] in aorta and pulmonary arteries from rabbits and rats, desmopressin caused dilation in the absence of vasopressin and in the presence of a selective V_1-antagonist. Furthermore, our experiments show that desmopressin did not affect the contractile responses to vasopressin. Therefore it is doubtful that the vasodilating action of desmopressin could be caused by competitive antagonism of the V_1-mediated vasoconstriction. It is more likely that these effects are caused by V_2-receptor activation.

In contrast, the V_1-V_2–antagonist desGly-d$(CH_2)_5$D-Tyr(Et)ValAVP did not show a significant effect on vasopressin-induced relaxation. Therefore it seems unlikely that the relaxant action of vasopressin on human saphenous veins is mediated by classic V_2-receptors. The reasons for this unexpected finding are not currently known. The V_1-V_2–antagonist desGly-d$(CH_2)_5$D-Tyr(Et)ValAVP exerts potent antagonistic effects on vascular contraction mediated through V_1-receptors.[8] Consequently, it is not established at present what side effects might result from the blockade of V_1-receptors. Before we can rule out the intervention of V_2-receptors in the vasopressin-induced relaxation, it would seem to be necessary to design V_2-antagonists that would not block the V_1-receptors. On the other hand, the effects of vasopressin could be indirect, resulting from the release of mediator(s) that induce dilatation. Among the potential mechanisms that could account for the dilatation in response to vasopressin, we have taken into consideration the possible intervention of the endothelial cell layer and the release of prostaglandins.

The vasopressin-induced dilatation after V_1-receptor blockade depends on the presence of an intact endothelium because it was absent in arteries denuded of endothelium. However, this endothelium-dependent relaxation does not involve the intervention of the L-arginine–nitric oxide pathway because L-NAME, a selective inhibitor of nitric oxide synthase, did not inhibit the vasopressin-induced relaxation. Because vasopressin stimulates the synthesis of prostaglandin I_2 by blood vessels,[33] it might be expected that cyclooxygenase inhibitors can modulate the responses to vasopressin. Our results show that indomethacin inhibits the relaxant effects of vasopressin. This strongly suggests that the effect is largely caused by the release of vasodilator prostaglandins from the endothelial cell layer.

In summary, our study shows that vasopressin and desmopressin dilate human saphenous veins through different mechanisms. The integrity of the endothelium seems to be essential to the observation of this effect. However, the endothelium-dependent relaxation to these peptides does not involve the intervention of the L-arginine–nitric oxide pathway. The vasopressin-induced relaxation requires previous blockade of V_1-receptors, appears to be mediated by the release of relaxant prostaglandins, is probably derived from endothelial cells, and is independent of V_2-receptor stimulation or nitric oxide formation. The effect of desmopressin is largely dependent on stimulation of V_2-receptors, which may bring about the release of dilating prostaglandins from the endothelial cell layer.

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Submitted May 1, 1996; accepted Aug. 17, 1996.