Relaxation of human isolated mesenteric arteries by vasopressin and desmopressin

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1 The effects of vasopressin and deamino-8-D-arginine vasopressin (DDAVP, desmopressin) were studied in artery rings (0.8–1 mm in external diameter) obtained from portions of human omentum during the course of abdominal operations (27 patients).

2 In arterial rings under resting tension, vasopressin produced concentration-dependent, endothelium-independent contractions with an EC_{50} of 0.59 ± 0.12 nM. The V_1 antagonist $d(CH_2)_5Tyr(Me)AVP$ (1 μ M) and the mixed V_1 – V_2 antagonist $desGly-d(CH_2)_5D-Tyr(Et)ValAVP$ (0.01 μ M) displaced the control curve to vasopressin to the right in a parallel manner without differences in the maximal responses. In the presence of indomethacin (1 μ M) the contractile response to vasopressin was significantly increased ($P < 0.01$).

3 In precontracted arterial rings, previously treated with the V_1 antagonist, $d(CH_2)_5Tyr(Me)AVP$ (1 μ M), vasopressin produced endothelium-dependent relaxation. This relaxation was reduced significantly ($P < 0.05$) by indomethacin (1 μ M) and unaffected by the V_1 – V_2 receptor antagonist $desGly-d(CH_2)_5D-Tyr(Et)ValAVP$ (1 μ M) or by N^G -nitro-L-arginine methyl ester (L-NAME, 0.1 mM).

4 The selective V_2 receptor agonist, DDAVP, caused endothelium-independent, concentration-dependent relaxations in precontracted arterial rings that were inhibited by the mixed V_1 – V_2 receptor antagonist, but not by the V_1 receptor antagonist or by pretreatment with indomethacin or L-NAME.

5 Results from this study suggest that vasopressin is primarily a constrictor of human mesenteric arteries by V_1 receptor stimulation; vasopressin causes dilatation only during V_1 receptor blockade. The relaxation appears to be mediated by the release of vasodilator prostaglandins from the endothelial cell layer and is independent of V_2 receptor stimulation or release of nitric oxide. In contrast, the relaxation induced by DDAVP is largely dependent on stimulation of V_2 receptors.

Keywords: Human mesenteric artery; vasopressin receptors; endothelium; nitric oxide

Introduction

Vasopressin acts directly on vascular smooth muscle to produce vasoconstriction through V_1 -receptor activation and promotes reabsorption of water in renal tubular cells through V_2 receptors coupled to adenylate cyclase activation (Michell *et al.*, 1979; Penit *et al.*, 1983). In addition it has been reported that vasopressin induces the release of adrenocorticotrophin through stimulation of V_3 (or V_{1b}) receptors located in the adenohipophysis (Jard *et al.*, 1986).

Further studies of the physiological 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 man and dogs (Liard & Spadone, 1984; Bichet *et al.*, 1988). In dogs, the mixed V_1 – V_2 receptor antagonist $d(CH_2)_5D-Tyr(Et)ValAVP$ inhibited the increase in cardiac output and fall in total peripheral resistance induced by the V_2 agonist, 4-valine, 8-D-arginine vasopressin (VDAVP) whereas the V_1 antagonist, $d(CH_2)_5Tyr(Me)AVP$ did not affect these haemodynamic responses (Liard, 1986). Since these effects persisted in anephric dogs (Liard, 1988) it was postulated that V_2 -like receptors exist in peripheral vessels. Furthermore, infusion of the V_2 agonist, deamino-8-D-arginine vasopressin (DDAVP, desmopressin) increased plasma adenosine 3':5'-cyclic monophosphate (cyclic AMP) concentration in normal subjects (Bichet *et al.*, 1989) and dogs (Liard, 1992) but a selective V_1 agonist did not. The increase in plasma cyclic AMP levels was prevented by pretreatment with a mixed V_1 – V_2 receptor antagonist but

was not affected by bilateral nephrectomy. These results suggest that V_2 receptors responsible for the increase in cyclic AMP are extrarenal (Liard, 1992).

Vasopressin produces constriction of isolated mesenteric arteries of the rat (Randall *et al.*, 1988), rabbit and guinea-pig (Vanner *et al.*, 1990). In the human mesenteric arterial bed, vasopressin causes powerful V_1 -mediated constriction in isolated mesenteric arteries (Ohlstein & Berkowitz, 1986) and in submucosal arterioles of the intestinal microcirculation (Vanner *et al.*, 1990). However, the possibility that vasopressin and DDAVP cause dilatation in human isolated blood vessels has not been defined. Accordingly, the present investigation was designed to determine directly the *in vitro* vascular response to vasopressin and DDAVP in human mesenteric arteries. Observations were made in the presence and absence of endothelium as well as with selective vasopressin receptor antagonists and inhibitors of cyclo-oxygenase.

Methods

Arterial segments were taken from portions of human omentum during the course of abdominal operations (27 patients, 11 men and 16 women, aged 32–61 years). The arteries 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 0.8 to 1 mm. In approximately 50% of the artery rings the endothelium was removed mechanically by inserting a roughened stainless-steel wire into the lumen and gently rolling the rings on wet filter paper.

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Two stainless steel pins 100 μm in diameter were introduced through the arterial lumen of the ring. One pin was fixed to the wall of the organ bath, while the other was connected to a force-displacement transducer (Grass FT03). Changes in isometric force were recorded on a Grass polygraph (model 7). Each artery ring was set up in a 4 ml bath containing modified Krebs-Henseleit solution of the following composition (mM): NaCl 115, KCl 4.6, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ 1.2, CaCl_2 2.5, NaHCO_3 25, glucose 1.1 and disodium EDTA 0.01. The solution was equilibrated with 95% O_2 and 5% CO_2 to give a pH of 7.3–7.4. 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 artery rings of similar length and outer diameter which were exposed repeatedly to 60 mM KCl. Basal tension was increased gradually until contractions were maximal. The optimal resting tension was 1 g. The artery rings were allowed to attain a steady level of tension during a 2-h accommodation period before testing. The contractile response to 60 mM KCl was similar in rubbed and unrubbed artery rings (2429 ± 172 versus 2534 ± 265 mg, $P > 0.05$). To study relaxation, artery rings were precontracted with 1–3 μM noradrenaline which gave a contraction ranging from 50 to 70% of contractions produced by 60 mM KCl.

Functional integrity of the endothelium was confirmed routinely by the presence or absence of relaxation induced by acetylcholine (0.1–1 μM) during contraction obtained with noradrenaline (1–3 μM). After each experiment the artery rings were carefully opened flat and stained with AgNO_3 to visualize the endothelium. Only results from rings with more than 70% of the endothelium were considered as control rings. Vessels in which the endothelium had been rubbed never showed more than 5% of their intima covered with endothelium.

Concentration-response curves for vasopressin were determined in a cumulative manner and control (in the absence of antagonists) and experimental (in the presence of antagonists) responses were obtained from separate vascular preparations. Vasopressin was applied in cumulative concentrations because preliminary experiments showed that noncumulative additions of vasopressin in these preparations produced similar effects than when vasopressin was applied in a cumulative fashion.

Following the equilibration period, concentration-response curves for vasopressin (0.01 nM–0.1 μM) were obtained in paired rings under resting tension in the absence and presence of either the V_1 antagonist $\text{d}(\text{CH}_2)_5\text{Tyr}(\text{Me})\text{AVP}$ (0.01 and 1 μM), the V_1 – V_2 vasopressin antagonist, $\text{desGly-d}(\text{CH}_2)_5\text{D-Tyr}(\text{Et})\text{ValAVP}$ (0.01 μM) or indomethacin (1 μM). To check the possibility that DDAVP is an antagonist of the V_1 receptor-mediated contraction, the effects of vasopressin were evaluated in the presence of 0.1 μM DDAVP.

To study vasopressin-induced relaxation, rings were incubated with the V_1 receptor antagonist $\text{d}(\text{CH}_2)_5\text{Tyr}(\text{Me})\text{AVP}$ and then contracted with 1–3 μM noradrenaline. After a stable contraction was obtained, concentration-response curves to vasopressin were determined in paired rings in the absence and presence of either the V_1 – V_2 receptor antagonist $\text{desGly-d}(\text{CH}_2)_5\text{D-Tyr}(\text{Et})\text{ValAVP}$ (1 μM), indomethacin (1 μM) or L-NAME (0.1 mM). Concentration-response curves to the V_2 agonist DDAVP (0.01 μM –0.1 μM) were also determined from a group of precontracted rings in the absence and in the presence of either the V_1 antagonist, the mixed V_1 – V_2 antagonist or indomethacin. As a control for each experimental group, at least 12 artery rings were contracted in a similar way to that described above and left untreated (without DDAVP or vasopressin addition to the bath). In these artery 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 min before the initiation of cumulative concentration-response curves to agonists. Only one concentration-response

curve to vasopressin or DDAVP was obtained in each artery ring.

Drugs

The following drugs were used: noradrenaline hydrochloride, acetylcholine chloride, indomethacin, N^G -nitro-L-arginine methyl ester hydrochloride (L-NAME), arginine vasopressin acetate salt, deamino-Cys D-arginine vasopressin acetate salt (DDAVP, desmopressin), $\text{d}(\text{CH}_2)_5\text{Tyr}(\text{Me})\text{AVP}$ [(1-(β -mercapto- β , β -cyclopentamethylenepropionic acid) 2-(O-methyl)-tyrosine, 8-arginine) vasopressin], $\text{desGly-d}(\text{CH}_2)_5\text{D-Tyr}(\text{Et})\text{ValAVP}$ [(1-(β -mercapto- β , β -cyclopentamethylenepropionic acid) 2-(O-ethyl)-D-tyrosine, 4-valine, 8-arginine, 9-desglycine) vasopressin], and sodium nitroprusside dihydrate (Sigma Chemical Co, St. Louis, MO, U.S.A.).

Drugs were prepared and diluted in distilled water except for indomethacin which was dissolved in absolute ethanol and sodium bicarbonate solution (150 mM) and readjusted to pH of 7.4 with HCl prior to use. Stock solutions of the drugs were freshly prepared every day.

Data analysis

EC_{50} values (concentrations of vasopressin producing half-maximal contractions) were determined from individual concentration-response curves by non-linear regression analysis, and from these values the geometric means were calculated. Relaxation was expressed as a percentage of the noradrenaline-induced contraction. All values are expressed as mean $\pm$ s.e.mean. In each experimental group n indicates the number of patients. At least 8 artery rings were obtained from each patient. Differences between agonist and antagonist-treated groups were assessed by one-way analysis of variance (ANOVA). Differences between means were identified by t test. Statistical significance was accepted at $P < 0.05$.

Results

Effects of vasopressin in artery rings under resting tension

Vasopressin (0.01 nM–0.1 μM) caused concentration-dependent contractions with an EC_{50} of 0.59 ± 0.12 nM. These contractions were endothelium-independent (Figure 1a). The presence of the V_1 antagonist, $\text{d}(\text{CH}_2)_5\text{Tyr}(\text{Me})\text{AVP}$, 0.01 μM , in the organ bath displaced the control curve for vasopressin 9 fold ($P < 0.05$) to the right in a parallel manner, but differences in the maximal tensions developed were not significant ($P > 0.05$). Increasing the concentration of $\text{d}(\text{CH}_2)_5\text{Tyr}(\text{Me})\text{AVP}$ to 1 μM further displaced (1525 fold; $P < 0.01$) the control curve for vasopressin (Figure 1a).

Arteries with and without endothelium exposed to 1 μM indomethacin did not show significant changes in resting tension as compared to arteries incubated in Krebs-Henseleit solution. However, the presence of indomethacin increased significantly ($P < 0.01$) both the maximal tension developed and the sensitivity to vasopressin (EC_{50} : 0.14 ± 0.05 nM) of artery rings with and without endothelium (Figure 1b). The mixed V_1 – V_2 receptor antagonist $\text{desGly-d}(\text{CH}_2)_5\text{D-Tyr}(\text{Et})\text{ValAVP}$ (0.01 μM) was also evaluated for its ability to antagonize vasopressin-induced contractions. This compound displaced the control curve for vasopressin 25 fold to the right ($P < 0.05$) in a parallel manner without differences in the maximal response. The presence of the V_2 agonist DDAVP (0.1 μM) did not affect the contractile responses to vasopressin (Figure 1b).

The specificity of the inhibitory effect of $\text{d}(\text{CH}_2)_5\text{Tyr}(\text{Me})\text{AVP}$ (1 μM) and $\text{desGly-d}(\text{CH}_2)_5\text{D-Tyr}(\text{Et})\text{ValAVP}$ (0.01 μM) on contractile responses was also studied in artery rings challenged with increasing concentrations of potassium chloride ($n = 3$) or noradrenaline ($n = 3$). The results showed that

Figure 1 Concentration-response curves for vasopressin determined in human mesenteric arterial rings. (a) Contractile effects of vasopressin in arterial rings with (●) ($n=5$) and without (○) ($n=4$) endothelium and in the presence of the V₁ antagonist d(CH₂)₅Tyr(Me)AVP (□, 0.01 μM; ■, 1 μM) ($n=5$). (b) Responses to vasopressin in the absence (●) ($n=5$) and presence of indomethacin (□) (1 μM) ($n=4$), the mixed V₁-V₂ antagonist desGly-d(CH₂)₅D-Tyr(Et)ValAVP (■) (0.01 μM) ($n=4$) or the V₂ agonist DDAVP (Δ) (0.1 μM) ($n=4$). Values are means $\pm$ s.e.mean.

contractions induced by these agents were not significantly different in the presence of the V₁ or the mixed V₁-V₂ antagonist.

Effects of vasopressin in precontracted artery rings

To determine whether vasopressin induces relaxation in precontracted arteries, increasing concentrations of this peptide were added to rings during submaximal contraction induced by noradrenaline (1–3 μM). Figure 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 0.1 mM 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.

In artery rings pretreated with the V₁ receptor antagonist d(CH₂)₅Tyr(Me)AVP, 1 μM and precontracted with noradrenaline (1–3 μM), vasopressin (0.01 nM–0.03 μM) produced concentration-dependent relaxations which were greater ($P < 0.05$) in arteries with endothelium than in endothelium-denuded rings (Figure 3a). At higher concentrations of vasopressin, relaxations changed to contraction, most probably produced by a displacement of the V₁ receptor antagonist from the V₁ receptors.

The mixed V₁-V₂ receptor antagonist desGly-d(CH₂)₅D-Tyr(Et)ValAVP (1 μM) was without effect on vasopressin-induced relaxation (Figure 3a). However, the presence of indomethacin (1 μM) reduced significantly ($P < 0.05$) the relaxation induced by vasopressin (Figure 3b). On the other hand, L-NAME (0.1 mM) treatment had no effect on vasopressin-induced relaxation. The same concentration of L-NAME abolished completely the relaxations to acetylcholine (0.1–3 μM) in artery rings with endothelium.

Effects of DDAVP

The selective antidiuretic agonist, DDAVP (0.01 nM–0.1 μM) did not produce significant changes in the resting tension of mesenteric arteries with ($n=4$) or without ($n=4$) endothelium (results not shown). In arteries contracted with

Figure 2 Contractile effects of vasopressin (VP) in arterial rings with and without endothelium precontracted with noradrenaline (NA, 3 μM). Sodium nitroprusside (SNP, 0.1 mM) caused almost complete relaxation of arterial rings.

noradrenaline (1–3 μM), DDAVP caused concentration-dependent relaxations which were similar in the presence and in the absence of endothelium (Figure 4a). Indomethacin (1 μM) did not modify the relaxations induced by DDAVP.

The specific V₁ receptor antagonist d(CH₂)₅Tyr(Me)AVP, 1 μM did not have a significant effect on DDAVP-induced relaxations (Figure 4b). In contrast, the V₁-V₂ receptor antagonist (desGly-d(CH₂)₅D-Tyr(Et)ValAVP, 1 μM) was a

Figure 3 Relaxation to vasopressin of arterial rings treated with the antagonist $d(CH_2)_5Tyr(Me)AVP$ ($1 \mu M$) and precontracted with noradrenaline ($1-3 \mu M$). (a) Concentration-response curves in the presence (●) ($n=4$) and absence (○) ($n=4$) of endothelium and in the presence of the V_1-V_2 antagonist $desGly-d(CH_2)_5D-Tyr(Et)ValAVP$ (▽) ($1 \mu M$) ($n=4$). (b) Relaxation to vasopressin in the absence (●) ($n=4$) and presence of indomethacin (Δ) ($1 \mu M$) ($n=4$) or N^G -nitro-L-arginine methyl ester (□) ($0.1 mM$). Values are means $\pm$ s.e.mean.

Figure 4 Relaxation to deamino-8-D-arginine vasopressin (DDAVP) of arterial rings precontracted with noradrenaline. (a) Responses to DDAVP in the presence (●) ($n=4$) and absence (○) ($n=4$) of endothelium and in the presence of indomethacin (■) ($1 \mu M$) ($n=4$); (b) responses to DDAVP in the absence (●) ($n=4$) and presence of the V_1-V_2 antagonist, $desGly-d(CH_2)_5D-Tyr(Et)ValAVP$ (Δ) ($1 \mu M$) ($n=4$) or V_1 antagonist $d(CH_2)_5Tyr(Me)AVP$ (□) ($1 \mu M$) ($n=4$). Values are means $\pm$ s.e.mean.

potent antagonist of DDAVP-mediated relaxation ($P < 0.05$). This antagonist did not affect the relaxations induced by acetylcholine ($0.1-3 \mu M$) or sodium nitroprusside ($0.01-1 \mu M$).

Discussion

The results of this study confirm previous reports showing that vasopressin is primarily a constrictor of human vascular smooth muscle due to V_1 vasopressin receptor stimulation (Lluch *et al.*, 1984; Ohlstein & Berkowitz, 1986; Martín de

Aguilera *et al.*, 1990). Our data also show that the vasopressin-induced contraction is not linked to the presence of an intact endothelium, thus indicating that vasodilator substances secreted by endothelial cells under basal, spontaneous conditions (Martín *et al.*, 1986) do not counteract the effects of vasopressin on smooth muscle cells.

The present investigation demonstrates that vasopressin elicits concentration-dependent relaxation in contracted human mesenteric arteries only during V_1 receptor blockade. Our results also show that DDAVP, a highly specific anti-diuretic V_2 receptor agonist (Manning & Sawyer, 1985), induced similar concentration-dependent relaxation to that

observed in response to the combination of vasopressin plus the vasoconstrictor antagonist. In contrast to the results described here, no evidence for the presence of V₂ receptor-mediated dilatation was obtained after application of vasopressin or DDAVP to isolated submucosal arterioles of the intestinal circulation of guinea-pigs, rabbits and humans (Vanner *et al.*, 1990). In addition to regional differences, it is possible that the size of the vessels used may be a factor in the response to DDAVP, as previously reported for vasopressin (Altura, 1975; Takayasu *et al.*, 1993).

In man, vasopressin causes direct, dose-dependent vasodilatation in the forearm, an effect which is augmented by the presence of V₁ receptor blockade (Hirsch *et al.*, 1989). Since infusion of DDAVP induced similar dose-dependent forearm vasodilatation to that observed in response to vasopressin, it was suggested that V₂ receptors were responsible for mediating these effects (Hirsch *et al.*, 1989). The link between V₂ receptor stimulation and cardiovascular effects was reported by Liard (1986) in conscious dogs showing that the V₁-V₂ antagonist d(CH₂)₅-D-Tyr(Et)AVP prevented the increase in cardiac output and fall in total peripheral resistance induced by a specific V₂ agonist. More recent experiments in dogs (Liard, 1994) suggest that V₂ receptor stimulation may trigger the release of nitric oxide since L-NAME, an inhibitor of nitric oxide synthase, attenuates the peripheral vasodilatation induced by injections of DDAVP.

Until now the possibility that vasopressin and DDAVP may dilate mesenteric vessels through V₂ receptors has not been investigated. Efforts to develop a specific V₂ antagonist have been unsuccessful (for review see László *et al.*, 1991). In this respect, all V₂ antagonists have a V₁ antagonistic effect as well (Sawyer & Manning, 1985). We used the mixed V₁-V₂ vasopressin antagonist desGly-d(CH₂)₅-D-Tyr(Et)ValAVP because it appears to be the most potent *in vitro* antagonist of human vasopressin-stimulated renal adenylate cyclase (Stassen *et al.*, 1984). It also antagonizes exogenous vasopressin-stimulated antidiuresis in conscious water-loaded rats (Kinter *et al.*, 1986). From a theoretical point of view, this analogue would be a highly potent specific vascular V₂ receptor antagonist. In the present experiments the mixed V₁-V₂ antagonist desGly-d(CH₂)₅-D-Tyr(Et)ValAVP prevented the relaxation induced by DDAVP, whereas the V₁ antagonist d(CH₂)₅Tyr(Me)AVP did not. These results suggest that the relaxation observed in response to DDAVP is mediated by a receptor similar to the renal V₂ receptor, a finding similar to that previously reported in dogs (Liard, 1986; 1988). In addition, because indomethacin treatment had little effect on DDAVP-induced relaxation, it is suggested that DDAVP-stimulated vasodilator prostaglandins synthesis under these experimental conditions seems unlikely. This interpretation is in agreement with results from human studies showing that indomethacin treatment did not influence the DDAVP-induced decrease in arterial blood pressure (Hasunuma *et al.*, 1991).

In contrast, the V₁-V₂ antagonist desGly-d(CH₂)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 is mediated by classical V₂ receptors.

The reasons for this unexpected finding are not presently known. The V₁-V₂ antagonist desGly-d(CH₂)₅-D-Tyr(Et)ValAVP exerts potent antagonistic effects on vascular contraction mediated through V₁ receptors. Consequently, it is not established at present what effects might result from the blockade of V₁ receptors. Before we can rule out the intervention of V₂ receptors in the vasopressin-induced relaxation it would seem necessary to design V₂ antagonists that would not block the V₁ receptors. On the other hand, the effects of vasopressin could be indirect, resulting from the release of mediator(s) inducing dilatation. Among the potential nonreceptor 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 V₁ receptor blockade depends on the presence of an intact endothelium since 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 since L-NAME, a selective inhibitor of nitric oxide synthase, did not inhibit the vasopressin-induced relaxation. Since vasopressin stimulates the synthesis of prostaglandin I₂ by blood vessels (Hassid & Williams, 1983) 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 due to the release of vasodilator prostaglandins from the endothelial cell layer. On the other hand, indomethacin potentiates the vasopressin-induced contraction in arteries with or without endothelium, thus suggesting that relaxant prostaglandins, derived mainly from smooth muscle cells, attenuate the V₁-mediated contractile effect of vasopressin.

We may conclude that the vasopressin receptor mediating contraction in human mesenteric arteries are of the V₁ type. A similar conclusion has been drawn from results obtained in isolated segments of human cerebral arteries (Martín de Aguilera *et al.*, 1990). In view of the specificity and potency of the V₁ antagonist d(CH₂)₅Tyr(Me)AVP, it seems appropriate to consider the use of blockade of V₁ receptors in those pathophysiological states characterized by an increased plasma vasopressin level. The physiological significance of the dilatation induced by vasopressin is not readily apparent because of the requirement of the V₁ blockade. Yet these effects may act to counterbalance V₁-mediated vasoconstriction.

In summary, our study shows that vasopressin and DDAVP dilate human mesenteric vessels through different mechanisms. The vasopressin-induced relaxation requires previous blockade of V₁ receptors, appears to be mediated by the release of relaxant prostaglandins and is independent of V₂ receptor stimulation or nitric oxide formation. The effect of DDAVP is largely dependent on stimulation of V₂ receptors predominantly located on smooth muscle cells.

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