Cellular Action and Interactions of Arginine Vasopressin in Vascular Smooth Muscle: Mechanisms and Clinical Implications

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ABSTRACT
In recent years, much has been learned about the vascular action of arginine vasopressin (AVP) including:
1. the structure, internalization, and recycling of the V1 AVP receptor;
2. the AVP postreceptor signaling events for the initial and sustained vascular smooth muscle cell contraction as well as the hormone's mitogenic effect;
3. the process of homologous and heterologous AVP desensitization in vascular smooth muscle cells;
4. the interaction of AVP with other vasoconstrictor and vasodilator hormones;
5. the vascular interaction of AVP with endothelial events; and
6. the vascular interactions that may occur with systemic acidemia or alkalemia as well as with ethanol. The various potential clinical and biochemical implications of these results are discussed briefly.

Key Words: Vasopressin, interactions, cellular mechanisms, vasorelaxing agents, vasoconstricting agents

Body fluid volume regulation involves a primacy of integrity of the arterial circulation, which can be compromised by either a diminished cardiac output or peripheral arterial vasodilation (see reference 1 for review). In such circumstances of "arterial underfilling," the nonosmotic release of arginine vasopressin (AVP) is accompanied by activation of the sympathetic and renin-angiotensin systems. Each of these constrictor systems has been shown to be important in mediating the hemodynamic compensation for arterial underfilling. In this regard, the use of specific AVP antagonists to the V1 vascular receptor has demonstrated an important constrictor role for AVP (Figure 1) in several experimental circumstances of arterial underfilling, such as hemorrhage, dehydration, adrenal insufficiency, cirrhosis, and cardiac failure (1). On this background, a series of studies have been performed in recent years to examine the cellular mechanisms of the vascular action of AVP, as well as its interaction with other vasoactive hormones and events on vascular smooth muscle. This review will summarize the results of these studies.

VASOPRESSIN RECEPTOR BINDING, PROCESSING, AND RECYCLING IN VASCULAR SMOOTH MUSCLE CELLS

Studies on AVP binding to rat vascular smooth muscle cells (VSMC) and displacement studies with a specific V1 AVP antagonist have revealed by Scatchard analysis a single class of V1 receptors in rat VSMC ($B_{max}$, $1.99 \times 10^{-12}$ mol/mg of protein; $K_d$, 2.15 $\times 10^{-9}$ mol) (2). Studies with fluorescein-labeled AVP (3) or $^3$H-labeled AVP (2) have shown significant internalization of the ligand-receptor complex. AVP receptor recycling to the surface occurs with a $t_{1/2}$ of 15 to 20 min at room temperature by a mechanism that does not involve the synthesis of new receptors or the existence of an intracellular pool of spare receptors (2).

Recently, the cloning of a cDNA encoding the rat V1 AVP receptor has been reported (4). This cDNA encodes a protein with seven putative transmembrane domains that binds AVP with affinities similar to those of the rat V1 receptor. This confirmation corresponds to that described for G protein-coupled receptors (5). The tissue distribution of the messen-
Figure 1. A molecular model of AVP showing the likely location of all atoms of the nine amino acids. The cleft, near the center bottom, is characterized by several oxygen atoms. This structural/atomic motif may be important for the binding of AVP to its receptor. This original figure was created by Professor Andre Haberli, University of Bern, Bern, Switzerland.

Figure 2. Hormone and second messenger interactions that mediate VSMC contraction in the presence or absence of endothelial cells. AVP or oxytocin binds to the vasopressin receptor, a protein with seven transmembrane domains. All and BK bind to separate receptors that are also proteins with seven transmembrane domains. These are schematically represented in this figure. The receptors for other vasoconstrictors such as BK and All are, like AVP, coupled to Gq and PLC. Once activated, PLC can initiate the generation of IP₃ and DAG. DAG stimulation can also be enhanced by PLD. IP₃ increases the release of Ca²⁺ (from sarcoplasmic reticulum (SR)), which promotes cell contraction. Vasoconstriction and vasodilation can be modified by several other physiological events (Figure 3). For example, vasoconstriction can be enhanced (+) by chronic ethanol treatment or depressed (−) by acute ethanol treatment. The increase in Ca²⁺ activates PLA2 (as does PKC) leading to AA and eventually to PGE₂ formation. PGE₂ via its AC coupled receptor attenuates vasoconstriction via cAMP, whereas AA directly stimulates (+) PKC, which inhibits Gq/PLC. PTH may also inhibit cell contraction via cAMP. PKC itself stimulates cell contraction. ANP (via GCyp) or NO (via GCys) increases cGMP, which inhibits (−) cell contraction. Finally, inhibition of Na/K-ATPase results in higher Na⁺, and potentially in reversal of the Na⁺/Ca²⁺ exchanger, leading to cellular Ca²⁺ accumulation and further rise in Ca²⁺. Cell K⁺ also falls with Na/K-ATPase inhibition. The accompanying decrease in membrane potential will also activate potential-operated channels. Increased intracellular (H⁺), i.e., ↓ pH, affected by changes in Na⁺/H⁺ exchange, attenuates cell contraction. In contrast, ↑ pH enhances cell contraction.

Abbreviations: BK, bradykinin; Gq, phospholipase C-related G protein; PLC, phospholipase C; PLD, phospholipase D; DAG, diacylglycerol; PC, phosphatidylcholine; P1, phosphatidylinositol; PI, phosphatidipid; PLB, phospholipase A₂; AA, arachidonic acid; PGE₂, prostaglandin E₂; Gs, G protein (stimulatory); AC, adenylate cyclase; Gs, G protein (inhibitory); PTH, parathyroid hormone; NO, nitric oxide; GCys, guanylate cyclase (soluble); GCyp, guanylate cyclase (particulate); Na⁺, sodium; H⁺, hydrogen; POC, potential-operated channel.
VSMC Contraction

Signaling Events in the Initial VSMC Contraction

As referred to above, the structure of the V₁ receptor corresponds to the conformation of G protein–regulated receptors (Figure 2) (5). In fact, a role for specific G proteins of the Gq class has been proposed in the case of other Ca²⁺-mobilizing hormones (16). In 1991, two alpha subunits of the Gq protein linked to the V₁ receptor signal transduction were immunologically identified in rat liver membranes (17); also, information has become available recently supporting the existence of a V₁-related Gq protein in VSMC (18). The putative G protein, which regulates the V₁ effects on Ca²⁺, does not appear to belong to the pertussis toxin–inhibitable subtype (19).

Beyond the G protein, the AVP-mediated activation pathway involves receptor-mediated breakdown of phosphatidylinositol 4,5-biphosphate (PIP₂) via phospholipase C, thereby generating inositol trisphosphate (IP₃), which acts as a secondary messenger for Ca²⁺ mobilization in VSMC (20,21). This effect of AVP also occurs in glomerular mesangial cells (GMC), which are similar morphologically and biochemically to VSMC (22,23). The resultant rise in cytosolic free calcium [Ca²⁺]j, which occurs within seconds after AVP-induced receptor activation, is independent of potential-activated calcium channels. As studied in VSMC and GMC, the major intracellular source of AVP-induced calcium release appears to be the endoplasmic reticulum (24). The AVP-induced rise in [Ca²⁺]j in VSMC is associated with an increase in Ca²⁺ efflux, which accounts for the rapid return of [Ca²⁺]j to near-baseline values. Ca²⁺ ATPase appears to be primarily involved in this AVP-induced Ca²⁺ efflux from VSMC, but there is also evidence for a role of increased Na⁺:Ca²⁺ exchange (24).

Signal Transduction in VSMC Cell Growth

AVP is known to be a mitogenic agent that can stimulate cell growth (34). The cell signaling for such an AVP effect in VSMC has recently been investigated. Because growth factors, such as epidermal growth factor, are known to cause tyrosine phosphorylation, the effect of AVP on this process in VSMC was examined with a specific phosphotyrosine antibody. AVP was found to induce tyrosine phosphorylation of a cytosolic 42-kd protein in both platelets (35) and VSMC (36). An inhibitor of tyrosine kinase, genistein, was further shown to inhibit this effect of AVP. This AVP-induced tyrosine phos-
phorylation appears to activate mitogen activated protein kinase, an important event in growth responses in VSMC (36). Further data are, however, needed to understand the exact mechanisms of the AVP interaction with the other VSMC growth factors.

HOMOLOGOUS AND HETEROLOGOUS VASOPRESSIN DESSENSITIZATION IN VSMC

Desensitization is a mechanism that may counteract the vasoconstricting properties of AVP and other pressor hormones. A rapid concentration-dependent homologous desensitization to AVP occurs in VSMC in culture (19). This homologous desensitization to the second dose of AVP occurs as early as 30 s after administration and is complete with an AVP first-dose concentration of 10^{-7} M. Receptor occupancy is only partially responsible for this AVP desensitization in VSMC. In addition, a significant role of protein kinase C activation has been suggested in the rapid homologous desensitization to AVP in VSMC (19). AVP receptor internalization can also be a factor in homologous AVP desensitization in VSMC (37).

Heterologous desensitization occurs when large concentrations of angiotensin II (AII) (10^{-6} M) are administered before an initial dose of AVP, causing a significant decrease in the effect of AVP to increase [Ca^{2+}]_i in VSMC (19). Similarly, AII desensitization occurs when VSMC were first incubated in the presence of high concentrations of AVP. In both cases, there is evidence of decreased intracellular Ca^{2+} stores after the first exposure to the desensitizing hormone. Long-term exposure to AVP can also produce a degree of heterologous desensitization, by an effect on postreceptor sites, such as protein kinase C activation, inositol lipids pools, and phosphatidylinositol kinase down-regulation (37).

Another variety of heterologous desensitization occurs in VSMC in association with protein kinase C activation by phorbol esters, which has been found to inhibit simultaneously AVP- and AII-induced IP_3 production and Ca^{2+} mobilization (38). Therefore, in this process of heterologous desensitization, the blocking process must occur at an activation site before IP_3 formation. Thus, this form of heterologous desensitization could affect hormone receptors, G proteins, or phospholipase C activity; protein kinase C-mediated phosphorylation of an IP_3 phosphatase may also occur and accelerate IP_3 catabolism. Recent evidence has given support to the hypothesis that protein kinase C-mediated phosphorylation of the V_1-related G protein is a critical mechanism to inhibit signal transduction (39). The presence of compartmentation in different membrane-related domains may help to explain the differences in homologous and heterologous desensitization found with phorbol esters and long-term or short-term exposure to AVP.

POTENTIATION OF VASCULAR EFFECTS OF VASOPRESSIN BY ANGIOTENSIN

As noted earlier, the nonosmotic release of AVP in circumstances of arterial underfilling, such as advanced cardiac failure, cirrhosis, adrenal insufficiency, and hemorrhage, is consistently associated with stimulation of the renin-angiotensin and sympathetic systems (1). There is evidence not only that plasma AVP and AII increase together, but also that these vasoactive hormones, when applied together, may exert an additive or synergistic effect on the in vivo pressor response (40) and on the contractile and Ca^{2+}-mobilizing response in cultured VSMC (41). In VSMC, each hormone binds to its specific receptor and then appears to stimulate IP_3 production from separate sources. In this regard, the possibility exists that the intracellular signal transduction differs for each pressor hormone by using different G protein assemblies, different subunits of phospholipase C, or a different pool of phospholipid molecules. This interpretation is consonant with the hypothesis that the phosphoinositide pool available for IP_3 generation is compartmentalized with only part of the total pool available to any given receptor. It seems likely that the VSMC interaction between AVP and AII at postreceptor signaling sites is shared with other vasoconstrictors, such as norepinephrine, endothelin, and thromboxane, which activate similar VSMC signaling pathways.

In experimental models of congestive heart failure in the rabbit (42) and renal vascular hypertension in the rat (43), lower degrees of activation of combined pressor systems may be more efficacious in causing systemic vasoconstriction than greater degrees of stimulation of any one pressor system. In human pathology, it is theoretically possible that an additive therapeutic effect to reduce cardiac afterload might be observed in cardiac failure patients treated with an angiotensin-converting enzyme inhibitor and with the recently described, orally active, nonpeptide V_1 AVP antagonist (44). In this regard, earlier studies with a peptide V_1 AVP antagonist given iv have shown that this is an effective approach in reducing cardiac afterload in advanced cardiac failure (45). A combination approach with an angiotensin-converting enzyme inhibitor and a V_1 AVP antagonist has yet not been examined in cardiac failure patients.

INTERACTION OFVASOPRESSIN AND ATRIAL NATRIURETIC PEPTIDE IN VSMC

In addition to the diuretic and natriuretic effects of atrial natriuretic peptides (ANP), these substances are also known to cause vasodilation. Moreover, plasma ANP concentrations are elevated early in cardiac failure and increase progressively as the severity of the heart failure worsens (46). At the same time,
the neurohumoral responses to arterial underfilling, i.e., plasma norepinephrine, ANP activity, and aldosterone and AVP concentrations, are progressively enhanced as cardiac failure worsens [1, 47]. The vascular interaction of vasoactive hormones with ANP is therefore of particular relevance to patients with cardiac failure. Although increases in plasma ANP may delay the onset of sodium retention in experimental cardiac failure [48], there is as yet little known about whether ANP attenuate the increased cardiac afterload caused by endogenous vasoconstrictors in advanced heart failure. The clinical study of this possibility awaits the availability of antagonists that are selective for the vascular and renal tubular epithelial effects of these ANP.

The cellular mechanisms whereby ANP block the contractile effect of AVP have been studied in VSMC in culture [49]. In these studies in VSMC, an ANP has been shown to decrease the AVP-induced early Ca2+ mobilization and shape changes by a cGMP-mediated mechanism. However, further experimental data have suggested that other effects of ANP on AVP-stimulated sustained VSMC contraction occur at a signaling site beyond the early acute IP3-mediated calcium mobilization in VSMC. Further evidence for this possibility has been recently obtained in studies that examined the effect of ANP on AVP-stimulated Na/H exchange [50]. Either ANP or a cell-permeable analog of cGMP was found to decrease the rise in pH and the enhanced sodium uptake observed in VSMC with AVP administration. Moreover, these effects of ANP were also obtained with amiloride and specific Na+/H+ exchange-blocking amiloride analogs. In vivo, the inhibition of Na/H exchange by amiloride causes vasodilation [51]. It thus appears that in AVP-stimulated VSMC, ANP not only interfere with early post-receptor activating pathways, but they also inhibit sustained contraction-related phenomena, such as the Na+/H+ exchange. It also seems likely that similar mechanisms are involved in the ANP-mediated attenuation of other vasoconstrictors.

INTERACTION OF VASOPRESSIN AND PARATHYROID HORMONE ON VSMC CONTRACTION

Plasma parathyroid hormone and AVP concentrations are known to be elevated in both acute and chronic renal failure. Thus, a potential vascular interaction between these hormones may occur in the setting of renal dysfunction. An increased incidence of hypertension does occur with primary hyperparathyroidism [52]. Moreover, in some tissues, such as proximal tubule epithelium, parathyroid hormone has been shown to cause polyphosphoinositides hydrolysis, a postreceptor signaling event that is the common accompaniment of VSMC contraction [53]. On the other hand, parathyroid hormone has been found to cause vasodilation and lower blood pressure [54].

In cultured VSMC cells, the predominant effect of parathyroid hormone was a dose-related increase in cAMP rather than evidence of PIP2 hydrolysis [9]. Parathyroid hormone, as well as the cell-permeant cAMP analog CIPheScAMP, decreased AVP postreceptor signaling as assessed by IP3 production, Ca2+ turnover, and VSMC contraction. This effect of parathyroid hormone was blocked by H8, an inhibitor of protein kinase A, but not by inhibition of prostaglandin synthesis. AVP modestly increased VSMC cAMP; this effect, however, was abolished by inhibition of prostaglandin synthesis. In this regard, AVP may stimulate arachidonate release by activation of phospholipases A2, C, or D [18, 55, 56]. As an indirect demonstration of this point, the inhibition of prostaglandin synthesis has been shown to enhance the contractile response of GMC to AVP [57].

Taken together, parathyroid hormone therefore appears to have the potential, by stimulating cAMP production, to attenuate the VSMC contractile response to AVP and other vasoressor agents that activate the PIP2 hydrolysis signal transduction pathway.

VASOPRESSIN AND OXYTOCIN RECEPTOR OCCUPANCY IN VASCULAR SMOOTH MUSCLE, MESANGIAL, AND MYOMETRIAL CELLS

AVP and oxytocin share the common property of causing contraction of VSMC, mesangial cells, and myometrial cells. A common receptor for AVP and oxytocin is not unreasonable because the structure of these two peptides differs by only two amino acids. On the other hand, separate receptors for oxytocin and AVP on these contractile tissues is a reasonable tenant, particularly because oxytocin, not AVP, is the mediator of labor and milk ejection. The development of selective V1 AVP and oxytocin receptor antagonists by Manning et al. [58] has allowed for the study of this issue in cultures of VSMC, mesangial cells, and myometrial cells.

Oxytocin causes contraction and Ca2+ mobilization of both VSMC and GMC in culture, but at higher threshold concentrations than AVP [59]. The responses to both AVP and oxytocin of VSMC and GMC are blocked by the V1 AVP but not the oxytocin antagonist. [3H]AVP binding studies on both contractile tissues demonstrated a concentration-dependent displacement with AVP and the V1 antagonist. However, oxytocin and the oxytocin antagonist only displaced the [3H]AVP binding at high concentrations (10^-6 M).

AVP caused a concentration-dependent contraction of myometrial cells, an effect that was blocked by the V1 AVP antagonist, but not by the oxytocin
VASCULAR INTERACTIONS OF VASOPRESSIN WITH ENDOTHELium-DERIVED RELAXATION FACTORS INCLUDING BRADYKININ, PROSTAGLANDINS, AND NITRIC OXIDE

Although bradykinin is a known vasodilator in vivo, the initial rise in 
Ca^{2+}, observed in VSMC with the application of this hormone mimics the initial signal transduction observed with vasoconstrictors (61). In vitro studies in VSMC have demonstrated that bradykinin mimics several additional postreceptor signaling events of AVP over a comparable concentration range. Specifically, both bradykinin and AVP increase contraction, IP_{3} production, 
Ca^{2+} efflux, and 
Ca^{2+} uptake and provoke a rise in pH in VSMC in the same dose-dependent manner (57). Both AVP- and bradykinin-stimulated VSMC contractile responses have been found to be mediated through a pertussis toxin-independent G protein (57). A role for vasodilating prostaglandins has also been demonstrated with both bradykinin and AVP, because the inhibition of prostaglandin synthesis with mep-}
fenamate has been shown to enhance the VSMC contractile response to both hormones (57). Thus, in VSMC, a potent vasoconstrictor, AVP, and a potent in vivo vasodilator, bradykinin, cause similar postreceptor signaling events, leading to contraction.

Major differences between these two hormones on endothelial cells in culture have, however, been shown. Specifically, bradykinin, but not AVP, stimulates endothelium-derived relaxing factor (EDRF), i.e., nitric oxide release (57); an interesting exception may occur at the central nervous system circulation, where AVP appears to have a vasodilatory effect through an L-arginine-related pathway (12). The bradykinin-stimulated EDRF release is sufficient to block totally the VSMC contractile response to maximal concentrations of AVP (10^{-6} M). In fact, a relaxation of VSMC in culture has been demonstrated with bradykinin-stimulated EDRF release, even in the presence of doses of up to 10^{-6} M AVP and bradykinin.

Thus, at least in rat VSMC in culture, bradykinin is a vasoconstrictor of equipotency with AVP in the absence of the endothelium. The in vivo vasodilatation of bradykinin therefore appears to be due to EDRF release from endothelial cells. The in vivo implications of these findings are that in the presence of endothelial abnormalities, such as those caused by an ischemic or septic insult, intravascular coagulation, diabetes, atherosclerosis, or untreated hypertension, bradykinin has the potential to become a vasoconstrictor hormone. Also, the critical role of the endothelial effects is highlighted by the different in vivo actions of AVP and bradykinin.

EFFECTS OF EXTRACELLULAR AND INTRACELLULAR pH ON VASCULAR ACTION OF VASOPRESSIN

Changes in acid-base status have been shown to alter vascular tone (62). Specifically, acidemia decreases vascular tone, whereas alkalemia is known to increase vascular tone. With respect to cellular mechanisms, acidosis has been shown to diminish the contractile response to catecholamines (62) and to alter calcium fluxes (63) and contractility in cardiac muscle (64).

Recent in vitro studies have focused on the effects of changes in both extracellular and intracellular pH on the VSMC response to AVP. As compared with a pH of 7.4, an extracellular pH of 7.0 was found to decrease [3H]AVP binding to VSMC and to decrease significantly the AVP-induced rise in 
Ca^{2+}; on the other hand, an extracellular pH of 7.8 was shown to increase AVP binding and 
Ca^{2+} mobilization in VSMC (30). These VSMC effects of extracellular pH were paralleled by similar changes in intracellular pH. Importantly, an extracellular pH of 7.0 decreased, whereas a pH of 7.8 increased, VSMC tone. Further studies with a proton ionophore, carbonyl cyanide m-chlorophenylhydrazone (CCCP), to change selectively intracellular pH allowed the effects of extracellular and intracellular pH on VSMC to be distinguished. The results demonstrated that a decrease in intracellular pH alone did not alter either AVP binding or the AVP-induced rise in 
Ca^{2+}. However, the effects of the decrease in intracellular pH with CCCP to diminish AVP-induced VSMC contraction were similar to those observed with an extracellular pH of 7.0. These in vitro studies therefore
suggest that, in addition to any direct effect of pH on vascular tone, extracellular acidemia and alkalemia may alter VSMC tone by changing the binding of vasopressor hormones to VSMC, with resultant alterations in Ca\(^{2+}\) mobilization and intracellular pH. The precise cellular mechanism whereby intracellular pH alters VSMC tone remains to be defined.

**EFFECT OF INHIBITION OF Na\(^{+}/K\(^{+}\) ATPase ON VASCULAR ACTION OF VASOPRESSIN**

A circulatory Na\(^{+}/K\(^{+}\)-ATPase inhibitor has been suggested to be of importance in the pathogenesis of essential hypertension (65) by increasing intracellular VSMC Na\(^{+}\) concentration and thereby enhancing Na\(^{+}/Ca\(^{2+}\) exchange and increasing Ca\(^{2+}\) in VSMC. The elevation in VSMC Ca\(^{2+}\) would then favor increased VSMC tone and thus arterial hypertension. Recently, an endogenous ouabain has been identified as at least one variety of circulating Na\(^{+}/K\(^{+}\)-ATPase inhibitors (66).

In *in vitro* studies have been performed to investigate whether ouabain enhances the response of VSMC to vasoconstrictors such as AVP (67). Preincubation with ouabain for 60 min enhanced VSMC contraction and increased both basal and AVP-stimulated [Ca\(^{2+}\)]. The effect of ouabain on AVP-induced Ca\(^{2+}\) mobilization was associated with increased VSMC Ca\(^{2+}\) accumulation and contraction. A second mechanism that appeared to be enhanced by ouabain was the phosphol ester–dependent, protein kinase C–mediated VSMC contraction (67). Ouabain was not found to alter [\(^{3}\)H]AVP binding or IP\(_3\) generation in VSMC. Of interest, the calcium channel blocker verapamil abolished the effect of ouabain to enhance the AVP-induced rise in VSMC [Ca\(^{2+}\)] and the contraction of VSMC. These findings suggest that the ouabain–associated membrane depolarization, which occurs in VSMC as intracellular K falls, may open potential-activated calcium channels rather than enhancing Na\(^{+}/Ca\(^{2+}\) exchange.

These *in vitro* VSMC studies thus have provided support for the possibility that a circulatory endogenous ouabain may enhance the VSMC tone in response to endogenous vasoconstrictors, such as AVP, AI, and norepinephrine, and may thereby contribute to the pathogenesis of essential hypertension. VSMC membrane depolarization and the opening of potential-activated Ca\(^{2+}\) channels by protein kinase C activation appear to be important cellular events mediating the effect of ouabain on VSMC.

**EFFECTS OF ACUTE AND CHRONIC ETHANOL EXPOSURE ON THE VASCULAR ACTION OF VASOPRESSIN**

Acute ethanol administration is associated with systemic vasodilation, whereas chronic ethanol abuse has been associated with a high incidence of hypertension. Recent *in vitro* studies have examined the cellular mechanisms whereby acute and chronic ethanol exposure alters the VSMC response to AVP (68). The results demonstrate that acute (30 min) ethanol exposure "down-regulates" potential-activated calcium channels, with attenuation of AVP-induced VSMC contraction. In contrast, chronic (3 to 4 days) ethanol exposure was found to "up-regulate" potential-activated Ca\(^{2+}\) channels with enhancement of AVP-induced VSMC contraction and Ca\(^{2+}\) uptake by voltage-sensitive Ca\(^{2+}\) channels. The decrement in AVP- and K-stimulated Ca\(^{2+}\) uptake in VSMC with the calcium channel blocker nifedipine was also enhanced by chronic ethanol exposure. Taken together, these *in vitro* results might suggest that the anti-hypertensive agent of choice in the hypertensive, alcoholic patient may be a calcium channel blocker.
SUMMARY

Although the primary vasoconstrictor considered in this review has been AVP, because of similar postreceptor signal transduction pathways, the various results have potential implications for other vasoconstrictors such as ANF, norepinephrine, thromboxane, and endothelin. In recent years, much has been learned about the vascular action of AVP including (1) the structure, internalization, and recycling of the V1 receptor; (2) the AVP postreceptor signaling events for the initial and sustained VSVMC contraction, as well as the hormone’s mitogenic effect; (3) the process of homologous and heterologous AVP desensitization in VSVMC; (4) the interaction of AVP with other vasoconstrictor and vasodilator hormones; (5) the vascular interaction of AVP with endothelial events; and (6) the vascular interactions that may occur with systemic acidemia or alkalalemia as well as with ethanol. Some of these interactions with AVP are shown in Figure 3. The various potential clinical implications of these results have been briefly discussed.

REFERENCES

27. Caramelo C, Okada K, Tsai P, Schrier RW:


53. Briner VA, Tsai P, Choong HL, Schrter RW:


64. **Kim D, Smith TW:** Altered Ca fluxes and contractile state during pH changes in cultured heart cells. Am J Physiol 1987;253:C137–C146.


