Clinical Conference

Pressor Systems in Hypertension and Congestive Heart Failure
Role of Vasopressin

Principal Discussant
Haralambos Gavras

Department of Medicine, Boston University School of Medicine and Boston City Hospital, Boston, Massachusetts

Elevated peripheral vascular resistance, which characterizes hypertension and congestive heart failure (the latter regardless of absolute blood pressure level) is maintained to a large extent by the combined effects of three major neurohormonal pressor mechanisms: the renin-angiotensin system, the sympathoadrenal system, and arginine vasopressin. Blockade of one of these mechanisms may lead to compensatory stimulation of the others, thus offsetting in part the hemodynamic benefits of a specific intervention. Combination therapy, designed to attack all three systems (with use of an angiotensin converting enzyme inhibitor, a sympathetic blocker such as clonidine, and an antagonist of the vasopressor action of vasopressin), may help in the treatment of such cases. To illustrate this strategy, two experimental studies, one case of malignant hypertension, and one case of congestive heart failure are presented. (Hypertension 1990;16:587-593)

It is generally recognized that a given level of arterial blood pressure is maintained to a large extent by the combined effects of three major neurohormonal pressor mechanisms: the renin-angiotensin system (RAS), the sympathetic nervous system (SNS), and arginine vasopressin (AVP). Several lines of experimental and clinical work over the years have demonstrated the participation of any one of these pressor mechanisms in the development and maintenance of various types of hypertension—or even in the maintenance of normotension. The first two, the RAS and the SNS, have been extensively investigated, and their research has yielded invaluable new treatments for hypertension and congestive heart failure that have now become part of the routine therapeutic armamentarium. The third, AVP, has long been known as the antidiuretic hormone that regulates fluid homeostasis. Only recently has it become the focus of experimental and clinical investigation as an important vasopressor mechanism with potential relevance in clinical situations characterized by elevated systemic vascular resistance such as hypertension and congestive heart failure. The fact that has recently stimulated research in this aspect of AVP was the development of AVP receptor antagonists by Manning's team.1,2 By using some of these antagonists, several investigators were able to demonstrate a pressor role for AVP in normotension,3 in maintaining blood pressure during hypovolemia,4,5 and in certain types of experimental hypertension.6

Our own earlier studies with the compound d(CH2)5-0-(Me)Tyr-AVP, revealed that the pressor function of AVP was most apparent on salt loading,7,8 was closely interrelated to those of the RAS and the SNS, and was maximized when the other two were impaired or eliminated.9,10 These findings were confirmed and amplified subsequently by other investigators.11,12 Because AVP analogues are known to have species-specific action, we set out to investigate the possible relevance of these findings in human pathophysiology. We took the above mentioned Vi antagonist through the various steps of pharmacological development to obtain an investigational new drug (IND) exemption number from the Food and Drug Administration (FDA) for its use in humans.13 With this new pharmacological tool, we attempted to clarify the interaction of the three pressor systems—the RAS, the SNS, and AVP—in human hypertension and congestive heart failure. The following two case reports illustrate a representative case each of hypertension and congestive heart failure, where elimination of the pressor action of AVP produced a definite, albeit transient, reaction.
hemodynamic improvement. These experiments were conducted according to protocols approved by the Institutional Review Board for Human Studies. Written informed consent was obtained from each subject before administration of the experimental agent.

**Case Reports**

**Patient 1**

M.P., a male black Haitian immigrant 36 years old, presented to the emergency room of Boston City Hospital complaining of severe headache, blurred vision, and nausea that had gradually worsened over the past 8–10 days. He had always been in good health, except for some weight loss in the last few weeks. The only other time he had been seen by a physician was about a year earlier when he had suffered a minor accidental injury on the job. At that time he was told that he had high blood pressure but attributed it to pain and anxiety, and as he had no health insurance, he failed to return for follow-up. He was admitted with a blood pressure of 260/155 mm Hg, heart rate of 96 beats/min, and grade IV retinopathy with flame-shaped hemorrhages, cotton wool spots, and blurred disc margins with no evidence of congestive heart failure and an otherwise normal physical examination. The first set of laboratory data included a hematocrit (Hct) 43%, white blood cell count (WBC) 5,400, potassium 3.8 mmol/1, sodium 142 mmol/1, blood urea nitrogen (BUN) 40 mg/dl, serum creatinine 1.9 mg/dl, and microscopic hematuria and proteinuria (+ + +). He agreed to participate in a research protocol to explore the effects of sequential elimination of pressor mechanisms. Accordingly he was connected to a blood pressure monitor and was first given 100 mg captopril orally with a glass of water on an empty stomach. Two hours later, he received a 0.3 mg oral dose of clonidine and 3 hours after that he received an intravenous dose of 0.5 mg of the antivasopressor AVP antagonist d(CH2)_5-0-(Me)Tyr-AVP. Blood samples for hormone measurements were drawn before each step. The results are shown in Table 1. The blood pressure hovered in the range of 144–150/96–100 mm Hg for about 1 hour after the AVP antagonist was administered and by 90 minutes had returned to 170/106 mm Hg. At the end of the protocol, the patient's blood pressure was treated with various drug combinations with only partial success but with substantial improvement of renal function tests. Eventually his blood pressure was controlled on a combination of hydrochlorothiazide, enalapril, and minoxidil.

**Patient 2**

P.C., an insurance businessman, presented in 1984 at age 59 with a history of hypertension of over 15 years' duration. Blood pressure had been reasonably well controlled whenever he was taking medication in the past, but he had been erratic in taking the medication and had discontinued treatment for long periods. He complained of a variety of side-effects, including lethargy, impotence, and Raynaud's phenomenon, evidently brought about by propranolol. His latest treatment had been clonidine (0.1 mg t.i.d.), which also controlled his blood pressure but caused drowsiness and dry mouth, both of which interfered with his ability to conduct business.

On examination he was a thin man, appearing older than his stated age. Blood pressure was 146/82 mm Hg in a sitting position, heart rate 76 beats/min and regular. The heart was enlarged, with intermittent S4 sound but no murmurs. The chest was clear, the abdomen protruding and slightly, diffusely tender. The liver was palpable, with normal consistency. Pedal pulses were diminished. Both upper and lower extremities were acrocyanotic. Pertinent laboratory findings were BUN 28 mg/dl, serum creatinine 1.8 mg/dl, uric acid 8.1 mg/dl, fasting glucose 135 mg/dl, cholesterol 298 mg/dl with high density lipoprotein 36 mg/dl, triglycerides 340 mg/dl, hematocrit 36%, with anisocytosis and hypochromia but otherwise normal blood counts and no iron deficiency. Urinalysis was normal. Electrocardiogram showed left ventricular hypertrophy by voltage criteria and nonspecific ST-T changes.

His medication was modified, with clonidine decreased to 0.1 mg at bedtime and the addition of indapamide (2.5 mg q.d.). Over the next several months his blood pressure remained well controlled at about the same range as before but with diminished dryness of mouth and minimal or no drowsiness. The only biochemical changes were a drop in serum potassium from 4.5 to 3.8 mmol/l and an increase in BUN to 32 mg/dl and uric acid to 8.4 mg/dl 6 months later. He was then lost to follow-up and returned again in late 1986 after 2 years. Four months earlier he had sustained a myocardial infarction, from which he had recovered uneventfully. He was initially treated with metoprolol but soon devel-

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**Table 1. Clinical Data on Patient 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>MBP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>AVP (pg/ml)</th>
<th>PRA (ng/ml/hr)</th>
<th>NE (pg/ml)</th>
<th>ΔMBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>236</td>
<td>146</td>
<td>176</td>
<td>94</td>
<td>2.4</td>
<td>1.3</td>
<td>296</td>
<td>...</td>
</tr>
<tr>
<td>Captopril</td>
<td>224</td>
<td>140</td>
<td>164</td>
<td>92</td>
<td>1.6</td>
<td>3.6</td>
<td>254</td>
<td>-12</td>
</tr>
<tr>
<td>Clonidine</td>
<td>168</td>
<td>102</td>
<td>124</td>
<td>80</td>
<td>2.2</td>
<td>2.4</td>
<td>128</td>
<td>-40</td>
</tr>
<tr>
<td>AVPI</td>
<td>144</td>
<td>96</td>
<td>112</td>
<td>84</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>-12</td>
</tr>
</tbody>
</table>

Blood pressure data denote levels at the peak effect of each treatment. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; AVP, arginine vasopressin; PRA, plasma renin activity; NE, norepinephrine; ΔMBP, difference in mean blood pressure from level of previous treatment; AVPI, AVP inhibitor.
oped chest wheezing and another Raynaud's attack, after which his treatment was changed to verapamil (80 mg t.i.d.). His blood pressure was well controlled on this regimen, and he felt quite well for a while, except for constant fatigue. He had not yet returned to work and was considering retirement but had been otherwise free of symptoms until about a week earlier when he started having severe pain in the right hypochondrium, abdominal bloating, and shortness of breath at the slightest exertion. On questioning, he also stated that he recently had difficulty lying in bed and had to be propped up on three pillows.

Physical examination revealed a blood pressure of 128/88 mm Hg, heart rate of 100 beats/min, considerable cardiac enlargement with an S3 gallop, moist rales in both lungs, a tender, firm liver enlarged to five or six fingerbreadths below the costal margin with rounded smooth edge, diffuse abdominal distension and tenderness, and pitting edema in the lower legs. A chest x-ray confirmed the presence of florid congestive heart failure. BUN was 45 mg/dl and serum creatinine 3.3 mg/dl; other blood tests were essentially unchanged, including the mild anemia.

He was admitted to the hospital, where verapamil was discontinued. He received repeat intravenous injections of furosemide and was placed on 2.5 mg enalapril, with blood pressures in the range of 120-130/68-80 mm Hg. His condition improved dramatically over the next few days, and he was eventually discharged on enalapril (5 mg q.d.) with no diuretics or other medications. He continued to improve steadily over the next 6 months, although at some point he required an increase of the enalapril dose to 10 mg q.d. and an addition of furosemide. He was then lost to follow-up again for another year and a half until he was brought to the emergency room with pulmonary edema. He was again admitted to the hospital, where verapamil was restarted. He received repeat intravenous injections of furosemide while his previous medications were continued, including enalapril (10 mg q.d.), clonidine (0.1 mg t.i.d.), and digoxin (0.25 mg alternating with 0.125 mg daily), which had been added elsewhere a few weeks earlier when his blood pressure had gradually increased and he complained of increasing dyspnea with minor effort. On admission, blood pressure was 110/74 mm Hg, heart rate 96 beats/min, and as before, he had an enlarged heart with S3 gallop and signs of congestive heart failure. As soon as he improved symptomatically and while he was in the intensive care unit with catheters in place for hemodynamic monitoring, he agreed to participate in a research protocol using the antivasopressor AVP antagonist d(CH2)5-0-(Me)Tyr-AVP at a single intravenous dose of 0.5 mg. Table 2 shows the most pertinent hemodynamic and hormonal data before and at the peak of hemodynamic change, which occurred at 15 minutes after injection of the AVP antagonist and returned gradually to baseline after 2 hours.

**Discussion**

In summary, patient 1 was a young black man with typical malignant phase hypertension and patient 2 was an older patient, with mild diabetes mellitus and long-standing, poorly controlled, essential hypertension that resulted in ischemic cardiomyopathy with congestive heart failure. What both had in common at the time of presentation was severe vasoconstriction with elevated systemic arteriolar resistance, even though one was extremely hypertensive and the other, during his last acute episode, was actually relatively hypotensive, as is often the case with patients in congestive heart failure. Both were treated with a sequential elimination of each one of the three pressor mechanisms: angiotensin converting enzyme (ACE) inhibition with captopril or enalapril, inhibition of the SNS with the α2-adrenergic receptor agonist clonidine, which activates central sympathoinhibitory neurons, and inhibition of the pressor V1 receptor-mediated vascular action of AVP. Each intervention produced a partial amelioration of hemodynamic parameters and, whenever obtainable, biochemical indexes of altered release or function of the other two systems.

In patients with accelerated or malignant hypertension, we have shown that the most important pressor component is the SNS-mediated vasoconstriction, the elimination of which resulted in an average 30 mm Hg fall in mean blood pressure.14 Next in magnitude is usually the RAS-mediated component, whose inhibition in the above study14 resulted in an average 15 mm Hg fall in mean blood pressure, whereas AVP inhibition produced an average fall of 9 mm Hg in mean blood pressure. However, black patients often tend to have suppressed plasma renin activity, even during malignant phase hypertension, as in the present case; our preliminary clinical studies suggest that the AVP-mediated pressor component may be more important in blacks.
than in whites in the pathophysiology of hypertension. Consistent with this notion, acute ACE inhibition in this patient produced a similar blood pressure fall to that of inhibition of the pressor effect of AVP. Regardless of possible racial differences, it appears from both experimental and clinical studies that the pressor contribution of each mechanism depends to a large extent on the effects of concurrent intervention on the other two major mechanisms. Indeed, compensatory neurohormonal changes may otherwise counteract or even totally offset the effects of the inhibition of one of the mechanisms.

The same process appears to be true in congestive heart failure as well. In a study of 10 such patients treated sequentially with the ACE inhibitor captopril, the \( \alpha \)-adrenergic antagonist phentolamine, and the same AVP inhibitor as above, we found the following: the SNS uniformly contributed to the elevated systemic vascular resistance of all patients by an average 34\% for the group because \( \alpha \)-adrenergic blockade produced systemic vasodilation in everyone. The RAS was activated in only half of the patients, and captopril decreased the systemic vascular resistance by an average 20\% for the whole group, but the effect was mostly observed in those with hyperreninemia. Plasma AVP concentration was elevated in only three patients, and these were the only ones to display a fall in systemic vascular resistance, which varied between 10\% and 25\% after a bolus of the AVP antagonist. Indeed, for the whole group there was a significant inverse correlation between baseline AVP levels and percent decline in systemic vascular resistance in response to the AVP antagonist (\( r = 0.70, p < 0.025, n = 10 \)). This is rather unusual, because in several other studies we found that the depressor response to a \( V_2 \) antagonist does not necessarily correlate with pretreatment levels of endogenous AVP, probably because the pressor contribution of AVP depends less on the absolute levels of the circulating hormone and more on the inability of counterregulatory mechanisms to compensate for the inhibition of the hormone. In other words, the depressor response from vascular antagonism of AVP is most pronounced when the RAS and the SNS have also been impaired, even though SNS impairment may quite often be associated with diminished AVP release.\(^{10,12}\)

It should be kept in mind, however, that AVP also exerts \( V_2 \) receptor-mediated effects and not only at the renotubular level (i.e., the classic antidiuretic action). Several pieces of evidence suggest that \( V_2 \)-like receptors may be located in the vascular wall and in the central nervous system and that both of these may well play a role in the regulation of vascular tone under various conditions.\(^{17,18}\) To date, there is no selective \( V_2 \) antagonist available to help elucidate their role in hypertension or heart failure. Experimental studies have relied on the use of almost pure \( V_2 \) agonists—\( dVDAVP \) or \( dDAVP \)—in hypertensive rat models with congenital AVP deficiency and on the use of dual \( V_1 \)-\( V_2 \) inhibiting compounds. By using such a dual \( V_1 \)-\( V_2 \) antagonist with somewhat greater \( V_2 \) than \( V_1 \), inhibiting potency in rats with pronounced left ventricular dysfunction due to ischemic cardiomyopathy, we could demonstrate a significant, though transient, hemodynamic improvement accompanied by greatly enhanced urinary output.\(^{19}\) Although these results are still preliminary and have not yet been duplicated in humans, they indicate that such a pharmacological tool, if available, should be of obvious benefit in congestive heart failure with hyponatremic edema.

There is a lot of experimental and clinical evidence in the literature indicating that AVP as a pressor hormone plays a particularly important role under conditions of salt loading.\(^{18}\) Salt-induced hypertension is characteristically associated with indexes of excessive central SNS stimulation, as well as systemic vasoconstriction. At the earliest stages of salt loading, a surge in AVP release apparently contributes to both the peripheral vasoconstriction, via its \( V_1 \) vascular receptors, and the excitation of central catecholaminergic neurons by a neuromodulatory action exerted via central vasopressinergic receptors. These receptors have not yet been clearly characterized but exhibit binding capacity to both \( V_1 \) and \( V_2 \) type ligands. To illustrate the role of AVP in linking excessive salt intake to sympathetic stimulation, we have proposed the "ignition key" theory: according to this theory, the initial surge of AVP after acute salt loading acts via descending vasopressinergic pathways from the periventricular hypothalamic region linked to the catecholaminergic neurons of the dorsal and ventrolateral medulla, thus setting in motion a sequence of events favoring a hyperadrenergic state.

It must also be recognized that, in addition to the three major pressor mechanisms, there are also numerous other vasoactive neurohumoral factors such as various tissue hormones or neurotransmitters that are locally generated within the vascular wall tissue or the central nervous system. Such vasoactive substances are closely interrelated to each other and may interact with each other's secretion or modulate each other's effects but are difficult to assess because they exert their action at their site of release and are rapidly inactivated on entering the systemic circulation. Examples of such substances include atrial natriuretic factor, bradykinin, prostaglandins, histamine, and serotonin, all of which have been shown to affect vascular tone and interact with one another. Attempts to dissect one system's effects may, by necessity, lead to "compartmentalization" and overinterpretation of experimental results, even when using intact conscious animals under conditions as close to normal as possible.

In conclusion, I have presented here two representative cases, one of malignant hypertension and one of benign essential hypertension, ischemic cardiomyopathy, and congestive cardiac failure, to illustrate a treatment strategy. In both cases, an important pathological characteristic was elevated systemic vascular resistance regardless of absolute levels of arterial blood pressure. In both, significant hemody-
namic and symptomatic improvement was achieved by sequential elimination of the three major pressor mechanisms: the sympathetically mediated vasoconstriction, the angiotensin-mediated vasoconstriction, and the vasoconstriction resulting from the pressor action of vasopressin. Without ignoring the vascular effects of other vasoactive mechanisms, I believe that combination therapy designed to attack all three major systemic pressor mechanisms may help in the rational treatment of pathological conditions characterized by elevated vascular resistance relatively refractory to conventional therapies.

Questions and Answers

Dr. Annette Fitz (University of Iowa, Iowa City, Iowa): I am trying to understand why pressure should fall when you block the V₁ receptor. Assuming that normal vasopressin is being secreted in these people, why don't the patients become hyponatremic? Are you dealing with a volume-contracted state or some other abnormality, or is there an abnormality in the vasopressin?

Dr. Gavras: I cannot tell you why they don't become hyponatremic because I have no long-term follow-up of what happens to the electrolytes. In humans, because of FDA limitations with our protocol, we can only test a single injection of the inhibitor. However, the V₁ receptor is not involved in water metabolism and antiduretic effect; it only mediates the pressor action of AVP. Therefore, I would not expect any changes in serum electrolytes, and indeed, we don't see any in our animal experiments.

Dr. Fitz: But if the vasopressin was high and the patients' intake was normal, I would expect them to have some degree of hyponatremia, unless something else was present. Blocking the V₁ receptor isn't going to block the effect.

Dr. Gavras: You are right, in cases of vasopressin excess one would expect to see hyponatremia. This is why we are trying to develop a compound with V₂-inhibiting properties, to see whether we can induce water diuresis in such cases. Just for the history, Smith Kline and French had a compound with combined V₁-V₂ receptor antagonistic properties, but it turned out to be an AVP agonist in humans. These compounds seem to have species specificity. Our compound with combined V₁-V₂-inhibiting properties has not yet been tested in doses adequate to determine its efficacy in humans. We have started with very small doses for fear of inducing severe dehydration in normal subjects. So far, with the highest doses tested, we have an equivocal response.

Dr. Michael Brody (University of Iowa, Iowa City, Iowa): I am reminded of the study by Thomas Unger that concerned the effect of a vasopressin antagonist in deoxycorticosterone acetate–salt hypertensive rats. Like several other groups, they did not find any effect on blood pressure, but their contribution was to identify a hemodynamic explanation, that is, a big increase in cardiac output prevented hypotension by offsetting the reduction in peripheral resistance. If you administer the vasopressin antagonist with a β-adrenergic receptor blocker, do you accentuate the hypotension?

Dr. Gavras: The findings of Unger are in agreement with our own experimental data in animals, which were treated with combined α- and β-adrenergic blockade. Under these conditions the blood pressure–lowering effect of the V₁ antagonist was greatly enhanced. Let me also clarify something else. The sympathetic component that mostly seems to interfere with the pressor action of AVP is the α₁-adrenergic receptor. If the α₁-adrenergic activity is impaired, AVP becomes a major pressor hormone. Baroreceptor stimulation also seems to attenuate the pressor action of AVP, something that has been known from animal experiments for many years.

Dr. Brody: I would have anticipated that the vasopressin antagonist would lower pressure more rapidly. Do you have any explanation for the delayed fall observed in your studies with rats?

Dr. Gavras: We speculate that there may be two different mechanisms involved: First, a rapid vasodepressor effect from direct inhibition of vascular V₁ receptors, which is seen in the rats, but that is rather transient in vivo because other pressor systems take over to restore blood pressure. If you combine the V₁ receptor inhibition with some sort of sympathetic inhibition and with inhibition of the renin-angiotensin system, the hypotensive effect lasts for at least 2 hours, maybe much longer. In humans, however, we have seen a second effect: the delayed orthostatic hypotension that occurs about 1–2 hours after injection of the V₁ antagonist. We have speculated that this may be a centrally mediated effect, via AVP receptors located in the central nervous system. In such a case the delay would represent the time needed for the AVP-inhibiting peptide to penetrate the central nervous system. If the sympathetic system is impaired and renin is suppressed, as is the case with many diabetics, vasopressin may be the only pressor mechanism maintaining blood pressure in the standing position.

Dr. George Hajduczok (University of Iowa, Iowa City, Iowa): You stated as a conclusion from your studies in humans that there was a ranking order to the maintenance of blood pressure, that is, the sympathetic nervous system contributes the greatest, followed by the renin-angiotensin system, then vasopressin. Can this conclusion be made without performing a randomized antagonist administration protocol?

Dr. Gavras: You are right, this is a flaw in our design, but it is difficult to overcome. When we administer the V₁ antagonist without prior interference in the other two systems, we see a minimal blood pressure fall in most cases. However, if we inhibit the sympathetic system with a large dose of clonidine (0.8 mg), which suppresses plasma norepinephrine to well under 100 pg/ml, there is always a pronounced fall in blood pressure. If we give an ACE inhibitor, there is a substantial fall in blood pressure in about 50% of the cases. Now, only if both sympathetic inhibition and angiotensin inhibition have preceded the initiation of AVP does this last step produce a
major blood pressure fall. That is why we have characterized AVP as the backup pressor system.

**Dr. Allyn Mark (University of Iowa, Iowa City, Iowa):** In the patients with heart failure, although several of the patients had elevated levels of vasopressin, the increases in plasma vasopressin were modest, less than 7 pg/ml, and in anesthetized animals and in normal conscious humans, if one infused vasopressin either systemically or in some cases locally in the vascular bed, one produced comparable increases in plasma vasopressin. The direct vasoconstrictor effects of those levels are negligible, so the question then is why does blockade of the V1 receptor in the presence of only very modest elevations of AVP seem to produce a decrease in vascular resistance and blood pressure in these patients with heart failure or hypertension?

**Dr. Gavras:** We have asked ourselves this same question. First of all, let me clarify that in congestive cardiac failure, there was a correlation between plasma AVP level and vasodepressor response to its inhibition. This is not unique to AVP. A long time ago I realized that plasma levels of a given hormone, although useful, do not necessarily predict the response to that hormone’s inhibition. There are several other factors that potentiate or attenuate the effect of a circulating hormone, such as the state of responsiveness of its receptors or the intracellular mechanisms, second messengers, and G proteins activated by the hormone. Changes in one or more of these components will affect the magnitude of the response to a given level of hormone or to its inhibition. I have learned this over the years by using antagonists to various vasoactive hormones. I have also learned that in vivo, the end result is the sum of the effects of the inhibition of one vasoactive system plus the concurrent compensatory changes in other vasoactive systems.

**Dr. William Lawton (University of Iowa, Iowa City, Iowa):** Also in relation to patients with congestive heart failure, does the level of hyponatremia in the patients studied give us a clue as to the vasopressin levels present or their response to the V1 antagonist?

**Dr. Gavras:** It probably does indicate inappropriately high antidiuretic hormone (ADH) secretion, but it does not necessarily predict the depressor response to V1 inhibition for the reasons I just mentioned. As you know, hyponatremia has been associated with more severe cardiac decompensation and worse prognosis. There are also a lot of other situations with inappropriate ADH secretion and dilutional hyponatremia. These are precisely the patients who would benefit from an AVP antagonist with V2-inhibiting properties. If the compound that we are now testing turns out to be effective in normal subjects, it might be expected to result in some increase in peripheral resistance. There may be other AVP receptors as well. For example, the vasopressin receptors of the central nervous system seem to have some binding characteristics of the V2 type and some of the V3 type. They have actually been referred to as V3 receptors, although the existence of a distinct third type of AVP receptor is not proven. The only way to demonstrate whether the central AVP receptors are different would be if they are cloned and characterized. As far as I know, no one has done it yet. It has been done, for example, for the a2-adrenergic receptor, and there is now evidence that there are two genes, suggesting the existence of two different types of a2-adrenergic receptors.

**Dr. Mark:** Would you comment on the adverse effects, or what you think might be the potentially adverse effects, of vasopressin antagonists based on your experience?
Dr. Gavras: We have not seen any adverse effects to the V₁ antagonist, and it has been extensively used in human studies for the last 5-6 years. But it has only been used in single doses. Experience with the combined V₁-V₂ antagonist is very limited in humans. Theoretically, if it has an excessive V₂ inhibitory effect, it might cause profound dehydration and hemoconcentration as has been seen in animals. This is why we have been overcautious, starting our testing at a very low dose and proceeding slowly.

Dr. Mark: I was interested in the observation that the V₁ antagonist briefly accentuated orthostatic hypotension in diabetics. Among other things, clinicians have been disappointed in the effects of administration of vasopressor drugs in treating patients with orthostatic hypotension and autonomic failure. Yet your data suggest that vasopressin may be playing a substantial compensatory role in this situation. Any ideas about how it is acting?

Dr. Gavras: As you know, vasopressin was proposed for the treatment of orthostatic hypotension due to autonomic insufficiency as far back as the mid 1950s by Braunwald. It is one of the recommended therapies for this condition. Doses that do not raise blood pressure in diabetes insipidus patients with an intact autonomic system tend to work in patients with impaired baroreceptor reflexes where the pressor effect of vasopressin is maximized.

Dr. Mark: Give us your thinking about the potential role of vasopressin antagonists in cardiovascular disorders in the long run.

Dr. Gavras: In congestive cardiac failure, I believe that there is a role for antivasopressor V₁ inhibition, especially in patients already receiving ACE inhibition and sympathetic inhibition, for example, with prazosin. There is no doubt in my mind that there is a role for V₁ inhibition that would result in water diuresis with minimal or no electrolyte disturbance, especially in cases associated with dilutional hypotremia. However, I don't know how successful we will be in developing this or any other compound with such properties in humans.

I also believe that vasopressin plays a role in the early stages of salt-induced hypertension by acting as a neurotransmitter or neuromodulator. It may be the ignition key that sets in motion a sequence of events that result in activation of the central sympathetic nervous system. If this is true, it may be important in initiating certain types of high blood pressure, especially those associated with salt overload.

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H Gavras

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