0031-6997/91/4301-0073$03.00/0
PHARMACOLOGICAL REVIEWS
Vol. 43, No. 1
Printed in U.S.A.

Pharmacology and Clinical Perspectives of Vasopressin Antagonists

FERENC A. LÁSZLÓ,* FERENC LÁSZLÓ, JR.,† AND DAVID DE WIED

Rudolf Magnus Institute for Pharmacology, University of Utrecht, Utrecht, The Netherlands

I. Introduction and Short Historical Overview

At the end of the 19th century, it was recognized that hypophyseal extracts exhibit vasopressor activity. The pressor activity of pituitary gland extracts was first observed by Oliver and Schaefer (1895). Three years later, this was confirmed by other investigators (Livon, 1898; von Cyon, 1898), and Howell (1898) demonstrated that the vasopressor principle resided in extracts of the posterior lobe. On the basis of these early observations the active material was named VP.‡ It is now clear that these experiments, performed using nonphysiological experimental conditions, led to a delay of more than 10 years in the recognition of the other dominant physiological role of the posterior pituitary, its antidiuretic effect. The discovery of this effect had its origin in clinical practice. Two physicians, Farini (1913) in Italy and von den Velden (1913) in Germany, independently reported the successful treatment of patients with diabetes insipidus by the injection of neurohypophyseal extracts. The administration of posterior pituitary extracts decreased the urinary output, increased the density of the urine, and reduced thirst. It is perhaps not generally known that the first observed kidney response to the administration of the posterior pituitary extract to anaesthetized animals was diuresis (Magnus and Schaefer, 1901; Schaefer and Herring, 1908).

Later, following the description of the antidiuretic

* Permanent address: Department of Comparative Physiology, Attila József University of Sciences, H-6701 Szeged, P.O.B. 533, Hungary.
† Permanent address: First Department of Medicine, Albert Szentgyörgyi, University of Medicine, H-6701, Szeged, Hungary.

‡ Abbreviations: VP, vasopressin; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; OT, oxytocin; LVP, lysine VP; dDAVP, 1-deamino-8-D-AVP; dAVP, 1-deamino-AVP; CRF, corticotropin-releasing factor; BP, blood pressure; DOCA, desoxycorticosterone acetate; OVP, ornithine VP; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; VAVP, 4-Val-AVP; SIADH, the syndrome of inappropriate antidiuretic hormone secretion; ACTH, adrenocorticotrophic hormone; Mca, mercaptocyclopentamethylene propionic acid; ECF, extracellular fluid.

effects of posterior pituitary extracts on the isolated kidney (Starling and Verney, 1924), the antidiuretic function of the neurohypophysis became the predominant aspect of interest. It emerged that VP was of great importance for the conservation of body fluid. For some years, studies concerning the vasopressor response were somewhat obscured by the interest in the dominant antidiuretic action. Only in the late 1920s was it established that the topical application of the posterior pituitary hormone to the capillary wall in vivo induced a constriction of the microscopic parts of the blood vessels in the web feet of the frog and the ears of the dog (Krogh, 1929), indicating that the hormone from the posterior pituitary exerts a constrictive effect on the peripheral blood vessels and plays a role in the blood flow regulation.

Only after the isolation and synthesis of VP (Turner et al., 1951; du Vigneaud et al., 1954) was it proved that the same hormone in the posterior pituitary is responsible for both antidiuretic and vasopressor effects. Following the synthesis of VP, the syntheses of analogues with at least the same activity as that of the natural hormone were reported (Berde et al., 1964; Berde and Boissonnas, 1968; Huguenin, 1964; Huguenin and Boissonnas, 1966; Zaoral et al., 1967; Zaoral and Sorm, 1966). Later attention was focused on analogues with a highly potent specific pressor or antidiuretic effect relative to that of the original hormone.

Pharmacological investigations of analogues with a selective pressor effect may be divided into those concerning whether the pressor activity of VP is of a physiological or pharmacological nature and those concerning whether, or to what extent, VP takes part in the homeostasis of the BP and affects the cardiovascular regulation (Saameli, 1968; Share 1976; Cowley, 1982; Johnston et al., 1983; Liard, 1984; Bennett and Gardiner, 1985) and vasoconstriction of regional blood vessels (Liard et al., 1982; Waeber et al., 1984; Liard, 1985; Undesser et al., 1985). Such studies led to the elucidation of the mechanism of VP action in different pathological states, e.g., in orthostasis (Davies et al., 1976, 1977; Zerbe et al., 1983), cardiac syncope (Davies et al., 1976; Baylis and Heath, 1977), and haemorrhagic and other shock states (Hershey et al., 1964, 1965, 1968; Mazzia et al., 1964; Altura et al., 1965a, 1966, 1970; Altura and Hershey, 1972; Altura, 1976a,b, 1980; McNeill, 1972; Zerbe et al., 1982a,b), and to the proposal of clinical uses.

As another approach, peptide chemists turned their attention back to the first studies of the administration of pituitary extracts to patients with diabetes insipidus and succeeded in preparing analogues superior in specificity and duration of antidiuretic effect to the natural hormone AVP in the treatment of diabetes insipidus, i.e., synthesizing drugs that are highly specific and have a prolonged antidiuretic effect. Finally, their efforts were crowned with success (Zaoral et al., 1967). VP analogues play an important role in molecular pharmacology, contributing insight into the mechanism of antidiuretic activity and the nature of the antidiuretic receptors (Butlen et al., 1978; Stassen et al., 1982, 1984, 1985).

The permeability functions of VP are initiated by interaction with specific receptors in the plasma membrane of responsive epithelial cells. These interactions result in stimulation of adenylate cyclase in the plasma membrane and increase of the cAMP concentration within the cell. On the basis of in vitro studies, Handler and Orloff (1981) described interactions between the antidiuretic effect of VP and the water permeability response to VP of prostaglandins, adrenergic agents, and adrenal steroid hormones. Prostaglandin E inhibits the water permeability response to VP of toad urinary bladder (Orloff et al., 1965) and of rabbit cortical collecting duct (Grantham and Orloff, 1968) through inhibition of the stimulation of adenylate cyclase activity of VP (Omachi et al., 1974). The inhibitors of the biosynthesis of prostaglandin E (Flores and Sharp, 1972; Albert and Handler, 1974) and antagonists of prostaglandin E (Albert and Handler, 1974) increase the water permeability response of the toad urinary bladder to VP. β-Adrenergic drugs imitate the effect of VP on water permeability and α-adrenergic agents inhibit the response to VP in frog skin (Bastide and Jard, 1968). The latter effects appear to be due to the inhibition of the stimulation of adenylate cyclase (Omachi et al., 1974). The adrenal steroid hormones increase the water permeability response to VP in the toad urinary bladder (Stoff et al., 1973; Zusman et al., 1978) and have a similar effect in the mammalian kidney. Adrenalectomy reduces the adenylate cyclase response to VP in the rat renal cortex and medulla (Rajerison et al., 1974), which appears to be the result of a reduction in the number of receptors for the hormone and reduced coupling of receptors to adenylate cyclase. The administration of aldosterone corrected only the decrease in the receptor number; treatment with dexamethasone corrected both defects.

More recently, attention has focused on the development of specific inhibitors of pressor or antidiuretic effects. As concerns development and characterization of VP antagonists, more comprehensive information can be found in recent reviews (Sawyer et al., 1981a; Schrier and Kim, 1984; Manning and Sawyer, 1985; Stassen et al., 1985; Manning et al., 1987a). The synthesis of selective pressor antagonists helps to elucidate the role of VP in a number of conditions such as experimentally induced hypertension (Crofton et al., 1979; Hatzinikolaou et al., 1980, 1981; Rabito et al., 1981; Okuno et al., 1983; Rascher et al., 1983; Hinojosa and Haywood, 1984; Cowley and Liard, 1987) or human hypertension (Gavras et al., 1984; Ribeiro et al., 1986; Hofbauer and Mah, 1987; Thibonnier, 1988) or in the study of interactions of VP with other systems, e.g., adrenal insufficiency (Schwartz et al., 1983; Elijovich et al., 1984; Ishikawa and Schrier, 1984), or in investigations of the mechanism of the

pressor or antidiuretic effect at the molecular (receptor) level (Guillon et al., 1982; Stassen et al., 1984, 1985).

Analogues inhibiting the antidiuretic effect of VP are of particular interest as possible therapeutic tools; for example, a strong antidiuretic antagonist could reverse the metabolic consequences of the enhanced secretion of VP in the Schwartz-Bartter syndrome (Schwartz et al., 1957; Schrier and Kim, 1984; Schrier, 1985; Kinter et al., 1985).

In this review, the use of VP antagonists in cardiovascular and renal physiology and pharmacology will be illustrated by presentation of examples of their applications in experimental animals. We deal mainly with the pharmacology of VP in whole animals or at the organ level, without going into its molecular mechanisms of action. Finally, we will examine the potential indications for the use of VP antagonists in human diseases and the results obtained through their use in human subjects.

II. Relationship of Chemical Structure and Biological Activity

A. Synthesis of Vasopressin Antagonists

The methodological development relating to synthetic VP analogues is associated with the names of two Nobel laureates. Vincent du Vigneaud and Robert Bruce Merrifield have had a profound impact on the synthesis and design of VP agonists and antagonists. Soon after the isolation and synthesis of VP (Turner et al., 1951; du Vigneaud et al., 1954), du Vigneaud and his colleagues explored the possibility of designing antagonists of their pharmacological action. Law and du Vigneaud (1960) reported that an OT analogue, in which the hydroxy group on the 2-tyrosine was methylated, blocked the vasopressor effect of AVP. A subsequent important finding was that the compound with two methyl groups on the β-carbon of the *l*-hemicystine of OT, (1-penicillamine) OT, was a weak antagonist of the pressor response (Schulz and du Vigneaud, 1966). The presence of two ethylene groups on the β-carbon in the 1-deamino-lys-VP was later observed to yield an analogue with significantly increased antivasopressor activity (Dyckes et al., 1974).

An important improvement was achieved through the introduction of new methodology by Merrifield. The Merrifield solid-phase procedure (Merrifield, 1963) has greatly enhanced the speed and efficiency with which analogues can be synthesized. Many more analogues can be synthesized in a shorter period than with conventional methods, thereby allowing promising clues to be followed up rapidly for the completion of an urgently required series of analogues. The development of the purification method that involves gel filtration on Sephadex G-15 in a two-step procedure (Manning, 1968) has also facilitated the rapid production of VP analogues. Recently, the wide-ranging application of high performance liquid chromatography has led to considerable development in the purification of synthetic VP analogues.

More information concerning the synthetic and purification methods used for the synthesis of VP agonists and antagonists can be obtained from a review by Manning and his coworkers (1981a). Outstanding work was produced by the peptide research group under Manning's guidance, and numerous useful biologically active VP antagonists were synthesized in their laboratory.

B. Bioassay and Definition of Antagonist Potency

New analogues of the posterior pituitary hormones are usually tested for their activities by standard biological assays. Basic bioassay techniques were described in detail by Stürmer (1968). We cannot deal with the whole series of bioassays used for determination of biological activities of VP analogues. Our discussion is limited to a few problems arising from the application of such standard bioassays to characterize novel analogues and to estimate antagonistic activities.

Pressor activity is established by intravenous administration of analogues into rats pretreated with an α-adrenergic or a ganglionic blocking agent (Dekanski, 1952; Stürmer, 1968). The vasopressor activities of the test compounds are compared with the response to a reference standard, such as AVP or LVP; pressor assays of the VP against the respective standards are quite precise and reproducible. Pressor activities may be expressed in terms of official units.

The estimation of antidiuretic activity is not as simple. Most of the tabulated antidiuretic activities derive from assays involving intravenous injections of analogues into ethanol-anaesthetized, water-loaded rats (Sawyer, 1958; De Wied, 1960). Some other investigators have reported activities determined by modifications of the Burn (1931) method. This assay involves water-loaded conscious rats, in which the analogues are injected subcutaneously and the time taken for the rats to excrete some specified fraction of the applied water load is determined.

Both methods can provide reliable estimations of the antidiuretic activity of VP analogues compared with a reference standard. However, the results of assays can equally be unreliable depending on the method design. It is known that the long-acting analogue, dDAVP, administered intravenously in small doses to ethanol-anaesthetized water-loaded rats, appears to have an antidiuretic response of about 1000 IU/mg (Vavra et al., 1968; Sawyer et al., 1974b). Because of its long-acting character, dDAVP appears to be much more potent when tested in Burn-type assays. In this case, the antidiuretic activity of dDAVP was determined to be about 100,000 units (Vavra et al., 1968; Sawyer et al., 1974a). Thus, it can be misleading to attempt to compare antidiuretic activities reported from different research centres using different assay designs. For correct characterization of the antidiuretic effects of VP analogues, it is important to deter-

mine the duration of the antidiuretic response, in addition to the biological activity in units per milligram.

The antagonistic potency of VP analogues is not so easy to determine. We generally use Schild's formula. Schild (1947) introduced the concept of pA_2 to express antagonistic potency. The pA_2 value is the negative logarithm of the molar concentration of an antagonist that reduces the response to a given dose of agonist until it is equal to the response to one-half that dose. Reliable pA_2 values can only be calculated from in vitro assays in which the molar concentration of the antagonist is known.

From the practical point of view, it is useful to attempt to estimate pA_2 values on the basis of in vivo methods. This requires unjustified assumptions that all antagonists have the same volume distribution, are eliminated at the same rate, and have similar access to, and solubility in, the vicinity of the receptors. It is surprising, therefore, that, in some cases in which in vivo and in vitro pA_2 values for pressor antagonists have been compared, they appear to be closely correlated (Keppens and De Wulf, 1979a). On the other hand, no clear correlation was found between in vivo and in vitro pA_2 estimates for antidiuretic antagonists (Butlen et al., 1978). Thus, in vivo assays for antagonistic activities remain essential as guides for the design of antagonists that could be of therapeutic value.

Manning and his coworkers (Manning et al., 1981a,b; Manning and Sawyer, 1982, 1983, 1985) first introduced the concept of "effective dose" estimated from in vivo pA_2 values by the method of Vavrek et al. (1972) and modified for rats by Dyckes et al. (1974). This is defined as the dose of the antagonist that reduces the response to the agonist to one-half of that of the same dose of agonist administered in the absence of the antagonist. In practice, this is done by finding the dose of antagonist that is higher or lower than the effective dose and estimating effective dose by interpolation on a logarithmic scale. The effective dose thus obtained is then divided by an assumed volume of distribution, 67 ml/kg, the estimated molar concentration of the antagonist, from which the in vivo pA_2 is calculated. On the basis of this calculation, it is obvious that the in vivo pA_2 values are only approximate estimates, but they do provide a convenient expression of relative potencies of antagonists.

C. Antagonists of the Pressor (V_1) Responses to Vasopressin

The most potent antagonists of the pressor response are analogues of dAVP which have (*a*) dimethyl[$(CH_3)_2$] , diethyl[$(C_2H_5)_2$], or cyclopentamethylene [$(CH_2)_5$] as substituents on the β carbon at position 1, (*b*) a basic amino acid at position 8, and (*c*) an O-methyl or O-ethyl substituent on the tyrosine at position 2. The latter, however, is not an absolute requirement for potent pressor antagonism. Thus, $d(CH_2)_5AVP$, with an antivasopressor pA_2 value of 8.35, is one of the most potent V_1 antagonists (Kruszynski et al., 1980). However, its O-methyl derivative, $d(CH_2)_5Tyr(Me)AVP$ is twice as potent (V_1 pA_2 = 8.62). This peptide has an antidiuretic activity of only 0.31 unit/mg and an anti-OT potency in vivo that is about 100 times less (OT pA_2 = 6.62) than its antivasopressor potency. The molecule does not display an antidiuretic antagonist response to AVP. Accordingly, $d(CH_2)_5Tyr(Me)AVP$ is one of the most potent and selective antivasopressor peptides reported to this date (Kruszynski et al., 1980). It has become the most widely used V_1 antagonist as a pharmacological tool in studies on the physiological and pathophysiological roles of VP. Its full chemical name is [(β-mercapto-β, β-cyclopentamethylene-propionic acid,2-O-methyltyrosine)]AVP, and the chemical stucture is depicted in fig. 1.

O-alkyl (methyl or ethyl) substituents at position 2 are highly potent V_1 antagonists. Many are, therefore, likely candidates for pharmacological tools in studies of the physiological and pathophysiological role. Recently, Manning et al. (1987a) reported 71 VP analogues, including those described above, which antagonize the vascular responses to VP. An additional six compounds from this list and their structural and biological characteristics are shown in table 1.

Finally, it is important to note that none of these 71 peptides antagonize the renal tubular (V_2) responses.

D. Antagonists of the Antidiuretic (V_2) Responses to Vasopressin

Efforts lasting more than 20 years were required for the discovery of the first effective antagonist of the antidiuretic (V_2) responses to both endogenous and exogenous VP (Manning et al., 1981b). Sawyer et al. (1981b) reported four V_2 antagonists, which have the following general structure (fig. 2). In table 1, these antagonists can be seen under numbers 1–4. These four analogues are partial agonists in that they produce a transient antidiuretic activity, followed by a longer period in which they inhibit antidiuretic responses to injected AVP. As can be observed in table 1, they are far from specific antidiuretic (V_2) antagonist compounds, because they are potent antipressors, and are antagonists of OT in vivo.

We most frequently use the fourth antagonist, $d(CH_2)_5Tyr(Et)^2Val^4AVP$, with an anti-$V_2$ pA_2 value of 7.57. Its anti-V_1 pA_2 value is 8.16. This shows that it is four times more potent as a V_1 antagonist than as a V_2 antagonist. When a combination of D-amino acids was introduced at position 2 and aliphatic amino acids at position 4, a really substantial enhancement of anti-V_2/V_1 selectivity (table 2) was produced (Manning et al., 1984b). Manning et al. (1987a) described 73 analogues that can antagonize the antidiuretic response to VP.

E. More Potent and More Selective Antagonists

Although it has long been known that vasopressor responses to VP are readily blocked, the synthesis of

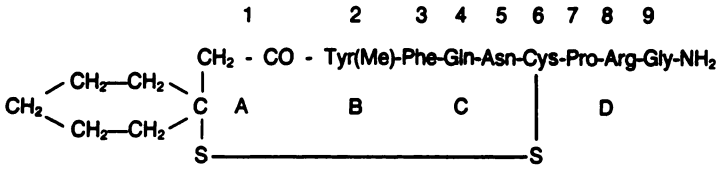

FIG. 1. Chemical structure of d(CH_2)$_5$Tyr(Me)AVP.

TABLE 1

*Chemical structures and biological activities of antagonists of vasopressor responses to VP**

Peptide	Chemical structure†				Biological activity		
	A	B	C	D	V_1 pA_2	OT pA_2	Antidiuretic activity units/mg
1. dEt_2AVP	$(C_2H_5)_2$	Tyr	Gln	L-Arg	8.36	7.30	0.38
2. dEt_2 D-Arg^{8}VP	$(C_2H_5)_2$	Tyr	Gln	D-Arg	7.96	6.95	0.067
3. d(CH_2)$_5$AVP	$(CH_2)_5$	Tyr	Gln	L-Arg	8.35	8.15 (6.79)‡	0.003
4. dPTyr(Me)^{2}AVP	$(CH_3)_2$	Tyr(Me)	Gln	L-Arg	7.96	7.61 (6.81)	3.50
5. dPVal^{4}D-Arg^{8}VP	$(CH_3)_2$	Tyr	Val	D-Arg	7.82	7.23 (6.29)	123
6. d(CH_2)$_5$Val^{4}D-Arg^{8}VP	$(CH_2)_5$	Tyr	Val	D-Arg	7.68	6.63 (6.23)	0.10

* References: Peptide 1 and 2, Manning et al. (1982b); 3, Kruszyinski et al. (1980); 4, Bankowski et al. (1978); 5, Manning et al. (1977); Lowbridge et al. (1978).

† See fig 1 for A–D.

‡ In vivo study.

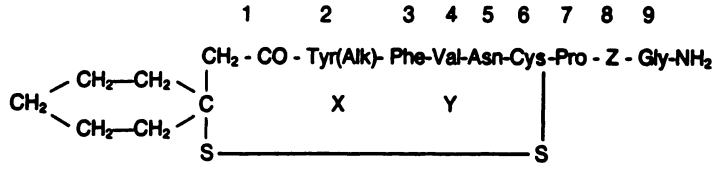

FIG. 2. General chemical structure of V_2 antagonists.

TABLE 2

*Antagonist of antidiuretic responses to VP**

Peptide	Chemical structure†			Biological activity			
	X	Y	Z	V_2 pA_2	V_1 pA_2	OT pA_2	V_1 ED/V_2 ED
1. d(CH_2)$_5$Tyr(Et)^{2}Val^{4}AVP	Tyr(Et)	Val	L-Arg	7.53	8.16	6.74	0.26
2. d(CH_2)$_5$Tyr(Me)^{2}Val^{4}AVP	Tyr(Me)	Val	L-Arg	7.35	8.32	6.94	0.094
3. d(CH_2)$_5$Tyr(Et)^{2}Val^{4}D-Arg^{8}VP	Tyr(Et)	Val	D-Arg	7.10	8.31	8.19	0.060
4. d(CH_2)$_5$Tyr(Me)Val^{4}D-Arg^{8}VP	Tyr(Me)	Val	D-Arg	6.68	8.44	7.51	0.019
5. d(CH_2)$_5$D-Tyr(Et)^{2}Val^{4}AVP	D-Tyr(Et)	Val	L-Arg	7.81	8.22	7.47	0.41
6. d(CH_2)$_5$D-Phe^{2}Val^{4}AVP	D-Phe	Val	L-Arg	8.06	8.06	6.92	0.87
7. d(CH_2)$_5$D-Ile^{2}Val^{4}AVP	D-Ile	Val	L-Arg	7.98	6.94	6.21	12.0
8. d(CH_2)$_5$D-Leu^{2}Val^{4}AVP	D-Leu	Val	L-Arg	7.79	6.45	6.05	22.0
9. d(CH_2)$_5$D-Ile^{2}Abu^{4}AVP	D-Ile	Abu	L-Arg	8.22	6.73	6.65	29.0
10. d(CH_2)$_5$D-Ile^{2}Ile^{4}AVP	D-Ile	Ile	L-Arg	8.04	6.43	6.90	39.0
11. d(CH_2)$_5$D-Ile^{2}Ala^{4}AVP	D-Ile	Ala	L-Arg	7.76	6.03	6.14	39.0

* References: Peptides 1–4, Manning et al. (1981b); 5, Manning et al. (1982c); 6–8, Manning et al. (1982a); 9–11, Manning et al. (1984b).

† See fig 2 for X–Z.

effective antagonists of the antidiuretic response remains an elusive goal. There have been substantial improvements in the design of specific antagonists, but it is evident that we have not yet succeeded in eliminating V_1 antagonism completely from the most specific V_2 antagonists. Most of the actions of VP on tissues other than the renal tubule appear to be mediated by V_1-type action.

Although the physiological importance of little, if any, of the nonvascular V_1 has been established, it would seem worth while to attempt to design V_2 antagonists that would not block the V_1 response. At present, one can only guess at what side effects might result from the blockade of V_1 receptors (section III.D) located at sites in the central nervous system, the anterior pituitary and other endocrine organs, the platelets, and the renal vasculature. Peptide chemists have engaged in extensive efforts to identify ways in which antagonists can be simplified, not only to increase the ease and economy of the synthetic work but also to identify structures that might be modified, perhaps by eliminating peptide bonds, to make orally active antagonistic analogues.

In terms of future studies we are faced with the chal-

lenge of designing and synthesizing a potent and truly specific V_1 antagonist devoid of oxytocic antagonism and of antagonism for other VP receptors. The results concerning the antagonists synthesized to date provide useful clues regarding the direction we must follow if we are to achieve this aim. However, the empirical approach must also be followed. For example, the most important V_1 antagonist, d(CH_2)$_5$Tyr(Me)AVP, should be modified in a variety of ways at positions 1–9, first with single modifications and later with appropriate combinations of substitutions and deletions. The results of these studies will doubtless provide useful clues for future design and may also yield a few surprises in terms of peptides displaying specificity for other VP receptors, e.g., they may lead to specific antagonists of VP receptors that mediate its CRF-like effect.

Much effort has been devoted to the development of the synthesis of a specific V_2 antagonist (Gash and Boer, 1987; Sawyer, 1988). Space constraints will not permit a full discussion of all the problems. Some of the key findings that have emerged are discussed in the following text.

Perhaps the most exciting finding arising from chemical structure-biological activity studies of VP antagonists was the discovery that the C-terminal glycinamide group could be deleted in full or in part and be replaced by a variety of L- and D-amino acids (L- and D-Ala, Ser, Arg, Phe, Ile, Thr, Pro) with no deterioration in antagonist potency (Manning et al., 1984a,c, 1987b). In these analogues, the modifications do not reduce the V_2 antagonistic potency and actually increase the V_2 antagonist specificity (Manning et al., 1987a). Deletion of the 7-proline does not always destroy the antagonistic activity (Huffman et al., 1985; Ali et al., 1986; Sawyer and Manning, 1988). In one analogue containing a 2-D-(O-ethyl) tyrosine, removal of the 7-proline did not alter the V_2 and V_1 antagonistic potencies (Manning et al., 1987c). This provides a good demonstration of how the structures within the ring can influence the effects that changes in the "tail" may exert on pharmacological activities.

V_2 antagonists appear to be remarkably tolerant to changes at the C terminal. A variety of amino acid amides may be substituted for the 9-glycinamide without compromising the antagonistic potency (Sawyer et al., 1988). Callahan et al. (1989) reported the synthesis of a series of VP antagonists in which part or all of the tripeptide tail was replaced by a simple alkyldiamine [$NH(CH_2)_nNH_2$] or an (aminoalkyl) guanidine [$NH(CH_2)_nNHC(=NH)\ NH_2$]. The results show that the entire tripeptide tail (Pro-Arg-Gly-NH_2) can be replaced by an alkyldiamine or an (aminoalkyl) guanidine without loss of biological activity. The same results could be achieved when the tripeptide tail was replaced by a dibasic dipeptide amide; e.g., Arg-Arg-NH_2 and Arg-Lys-NH_2 attached directly to the cyclic hexapeptide ring are potent V_2 antagonists (Ali et al., 1987).

When the 9-tyrosinamide is substituted, this residue can be radioiodinated by standard methods for the performance of radiolabeled receptor ligand experiments (Jard et al., 1987a). To examine the role of the disulphide ring in VP antagonists and in an attempt to prepare analogues with increased metabolic stability, dicarba analogues were prepared in which the disulphide bond was replaced by two methylene groups. These dicarbavasopressin analogues retained the antagonist potency in vitro and in vivo (Moore et al., 1988).

Essentially all of the hundreds of posterior pituitary hormone analogues that have been synthesized, both agonistic and antagonistic, contain a ring structure. Manning et al. (1987d) reported that acyclic analogues of some V_2 or V_1 antagonists retained substantial antagonistic potency. In fact, there is one acyclic peptide [fig. 3 (*1*)] among the most potent V_2 antagonists so far reported. However, the acyclic form of the most specific and potent V_1 antagonist, d(CH_2)$_5$Tyr(Me)AVP, has a vasopressor antagonists potency about 97% less than that of the cyclic form [fig. 3 (*2*)]. This modification would appear to be another good example of the importance of the constituents in the ring, particularly at the 2 and 4 positions, in determining the effects of structural changes on antagonistic activities. Furthermore, the linear peptides are much easier to produce than cyclic peptides and the yields are better. They also offer us the opportunity to explore further simplifications and modifications aimed at the synthesis of antagonistic molecules that are more stable and, thus, potentially orally active. These are very important considerations in the design of antagonists for possible clinical introduction. Recent findings (Manning et al., 1988; Manning and Sawyer, 1989) prove conclusively that a ring structure is not a requirement for recognition of or for binding to V_2 or V_1 receptors. This discovery thus offers a promising new approach to the design of peptide and non-peptide antagonists of AVP and perhaps the other cyclic peptides such as somatostatin, atrial natriuretic factor, insulin, and the recently discovered endothelin.

III. Physiological and Pathophysiological Roles of Vasopressin Antagonists

A. Role of V_1 Antagonists in Central and Peripheral Circulation

1. General circulation: blood pressure regulation. After the discovery of the antidiuretic action of VP (Farini, 1913; von den Velden, 1913; Starling and Verney, 1924), the antidiuretic role of the neurohypophysis became the predominant aspect of scientific interest relating to VP. It was clear that this hormone was vitally important for the conservation of body fluids and that, although its pressor effect was widely observed, this action required amounts far in excess of that needed for maximal antidiuretic activity (Saameli, 1968; Sawyer, 1971; Nakano, 1974). During the last few years, VP has been gaining

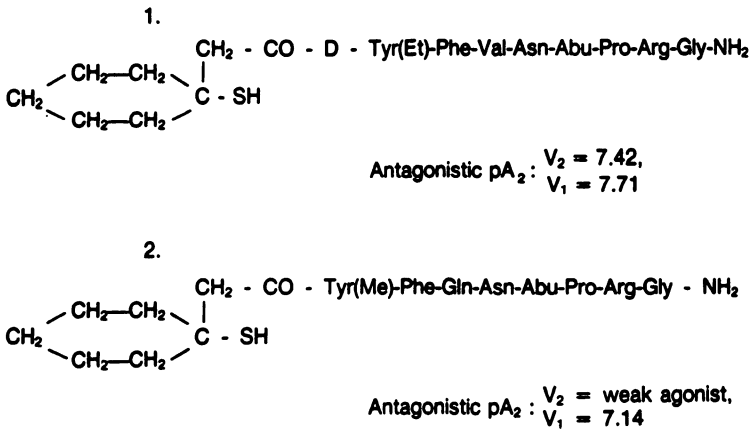

FIG. 3. V_2 and V_1 antagonists with opening rings.

recognition as an important factor in normal BP regulation. Both physiological and near-physiological VP levels have been shown to help maintain the BP and to influence the heart rate and cardiac output under different conditions.

Many important observations were needed to establish this hypothesis: (*a*) the pressor sensitivity to VP is greatly enhanced in the absence of baroreceptor reflexes (Cowley et al., 1974); (*b*) this enhancement of pressor sensitivity was much higher than that seen with other pressor agents (angiotensin, norepinephrine) (Cowley and de Clue, 1976; Cowley, 1978); (*c*) after a sensitive radioimmunoassay had been developed (Husain et al., 1973; Robertson et al., 1973; Skowsky et al., 1974; Mohring and Mohring, 1975), it could be demonstrated that the changes in circulating VP concentrations were enough to influence blood haemodynamics.

In samples obtained after overnight fasting, the plasma AVP of normally hydrated human subjects has been typically observed to range between 2 and 4 pg/ml (Cowley et al., 1981a, 1985; Cowley and Barber, 1983). In rats, the AVP level lies in the range of 3–10 pg/ml after rapid decapitation (Cowley, 1982; Brunner et al., 1983). Water deprivation (24–35 h) in humans with a normal sodium intake results in a plasma AVP level of about 10 pg/ml (Morton et al., 1975; Cowley et al., 1981b). Water restriction in dogs receiving a high-sodium dry-food diet can increase the plasma AVP to within the range 20–40 pg/ml (Cowley et al., 1981a). The most dramatically elevated AVP levels have been observed following syncope, traumatic surgical procedures, and hypotensive haemorrhage. The last situation may result in plasma AVP concentrations of 100–500 pg/ml (Arnauld et al., 1977; Robertson, 1977; Cowley et al., 1980; Weitzman et al., 1980).

The direct observation of blood vessels allowed investigators to evaluate the effective vasoconstrictor concentrations of AVP. The contraction of isolated rat aortic smooth muscle cells has been observed at concentrations of about 10 pg/ml (Penit et al., 1983). Altura (1975) reported that a similar concentration of AVP (as low as 10 pg/ml) elicited a detectable vasoconstriction in mesenteric microvessels of the rat.

BP determinations are a notably poor vasoconstrictor index in animals with intact reflex control of the circulation and particularly so for detecting the effects of VP. Measurements of BP in animals lacking autonomic reflex control mechanism, or the determination of peripheral vascular resistance and cardiac output in normal animals, have provided more useful indices of vasoconstriction. The ability of intravenously infused AVP to increase plasma AVP levels and arterial pressure has been demonstrated in both unanaesthetized animals and humans. Plasma AVP levels of nearly 50 pg/ml must be attained before a statistically significant increase in mean arterial pressure is achieved in normal conscious dogs and humans (Cowley et al., 1980; Mohring et al., 1980; Montani et al., 1980). Significant decreases in cardiac output occurred at physiological plasma levels of AVP without changes in the arterial pressure (Montani et al., 1980; Ebert et al., 1986; Osborn et al., 1987). Baroreceptor mechanisms appear to contribute to the reduction in cardiac output in conscious dogs, because the decrease is greatly blunted following sinoaortic baroreceptor denervation (Cowley et al., 1974; Montani et al., 1980). As consequences of sinoaortic baroreceptor denervation, unanaesthetized dogs exhibited a lowered VP threshold sensitivity (11-fold), and the overall pressor sensitivity was enhanced to 6–100 times the normal level (Cowley et al., 1974). Similar observations were made in conscious rabbits with baroreceptor denervation (Undesser et al., 1985).

Accordingly, V_1 antagonists may decrease the systemic vascular resistance and increase the cardiac output without affecting BP (Rascher et al., 1985). Thus, the absence of a hypotensive response to a V_1 antagonist does not necessarily indicate that endogenous AVP does not exert vasoconstrictor effects; moreover, the fact that the vasoconstrictor effects of VP show marked regional differences should be take into account (Liard et al., 1982; Altura and Altura, 1984; Liard, 1985). This is reflected

by a predominant effect of V_1 antagonists in AVP-sensitive vascular beds such as the blood vessels in the intestines and the skin (Charocopos et al., 1982; Pang, 1983; Wood et al., 1983). Measurements of haemodynamic parameters might, therefore, reveal effects of V_1 antagonists, even if no changes in the systemic haemodynamics are observed. However, the alterations in regional blood flow established after intravenous administration of a VP agonist may also be influenced by counterregulatory mechanisms. When VP was injected directly into the arteries of various organs, the changes in blood flow were markedly different from those seen after intravenous administration (Liard, 1985).

The synergistic effect of norepinephrine, angiotensin II, and VP could also modify the VP response (Altura et al., 1965b; Bartelstone and Nasmyth, 1965; Commarato and Lum 1969; Gerke et al., 1977). It has been reported that angiotensin II and isoproterenol in mildly pressor amounts decrease the pressor responses to VP in the conscious rat (Burnier and Brunner, 1983; Elijovich et al., 1984). This mechanism can counteract the hypotensive and vasodilator effects of V_1 antagonists, including activation of the renin-angiotensin system and the sympathetic nervous system. V_1 antagonists may be ineffective or induce only a small and transient decrease in the BP if both systems are intact. After blockade of angiotensin production with converting enzyme inhibitors or angiotensin II receptor antagonists or after the administration of sympatholytic drugs, a significant and prolonged hypotensive response can be observed following V_1 antagonist treatment (Andrews and Brenner, 1981; Gavras et al., 1982; Houck et al., 1983; Schwartz and Reid, 1983; Hiwatari et al., 1985). Haemodynamic effects of selective V_1 antagonists in dehydrated dogs were different from those of a combined V_1 and V_2 antagonist (Liard, 1986), indicating that some of the haemodynamic effects of endogenous AVP remain unblocked after the administration of a V_1 antagonist.

It is well known that VP plays an important role in the immediate defense against blood volume depletion. Frieden and Keller (1954) reported that dogs with diabetes insipidus were more susceptible to haemorrhage than normal dogs. Using Brattleboro homozygous rats, Laycock et al. (1979) observed that, following controlled blood losses, the BP was significantly lower in rats with diabetes insipidus than in nondiabetic controls. After haemorrhage (16.7 ml/kg blood loss over 5 min), rats with diabetes insipidus exhibited a slower BP recovery than did control animals (Zerbe et al., 1982a,b). Gardiner and Bennett (1982) observed that less blood needed to be withdrawn from Brattleboro rats to achieve a given BP reduction. Similar results were obtained by using V_1 antagonists. Rascher et al. (1983) and Gregory et al. (1988) described in detail that V_1 antagonists could not induce a significant decrease in BP of conscious rats because of the buffer action of the baroreceptor reflex. In conscious dogs, Schwartz and Reid (1981) determined that a 15-ml/kg blood loss over 15 min caused no hypotension response and did not change the heart rate. Following V_1 antagonist administration, the same haemorrhage rate decreased the mean arterial pressure from 96 to 64 mm Hg and increased the heart rate from 71 to 130 beats/min. Pang (1983) stated that the administration of a V_1 antagonist, following hypotensive haemorrhage, reduced the mean arterial pressure and increased the percentage of distribution of the cardiac output to the skin and gastrointestinal tract. The restoration of the BP toward baseline values proved to be impaired after haemorrhage in rats treated with VP antagonists (Cowley et al., 1980).

The osmolar changes in dehydration are far more important than volume in determining AVP level increases under normal conditions (Robertson, 1977; Quillen and Cowley, 1983). In prolonged dehydration, the plasma AVP level can increase from 10 to 30 pg/ml; these levels appear to be associated with noteworthy haemodynamic effects, depending on the experimental conditions. Woods and Johnston (1983) found evidence that AVP was essential for the maintenance of BP during fluid deprivation in rats, but Rockhold et al. (1984) found no effect of a VP antagonist on the BP in similar situations. Other authors reported that a V_1 antagonist led to a moderate or a transient decline in BP following dehydration (Andrews and Brenner, 1981; Aisenbrey et al., 1981; Burnier et al., 1983; Brand et al., 1988). When an antagonist or angiotensin II (Andrews and Brenner, 1981), an inhibitor of the converting enzyme (Burnier et al., 1983), or propranolol (Schwartz and Reid, 1983) was administered in water-deprived rats, the V_1 antagonist lowered the BP further and the decrease was not as transient. These results demonstrate an important role of VP in BP regulation during water deprivation and provide additional evidence that the maintenance of arterial pressure observed after VP blockade in water-deprived animals is dependent on activation of the sympathetic nervous and renin-angiotensin systems.

Because the cardiac output and heart rate increased well beyond the predehydration control values following V_1 antagonist administration, the possibility that these effects are not completely explained by suppression of VP-induced vasoconstriction must be considered. These effects could be related to the haemodynamic consequences of an interaction with the V_2 response (Schwartz et al., 1985a). Liard (1986) proved this hypothesis by comparing the haemodynamic effects of a V_1 antagonist and a V_2 antagonist in dehydrated dogs. The increases in cardiac output and heart rate were significantly smaller when the V_2 antagonist was also administered.

In conscious animals, hypotensive effects of V_1 antagonists have also been observed after hyperosmotic hypovolaemia induced by glycerol administration (Hofbauer et al., 1982, 1984a) and in severe potassium deple-

tion (Paller and Linas, 1983). During adrenocortical insufficiency, decreased plasma volume and arterial pressure have been observed. The plasma AVP level increased from 4 to 15 pg/ml and the BP was reduced by 20 mm Hg after the injection of $d(CH_2)_5Tyr(Me)AVP$ in dogs (Schwartz et al., 1983).

The involvement of VP in maintaining the BP in adrenal insufficiency has also been determined in rats (Elijovich et al., 1984; Ishikawa and Schrier, 1984; Ishikawa et al., 1985). In contrast with its involvement in short-term BP control, which is now firmly established, the roles of VP in the long-term regulation of arterial pressure and in hypertension remain controversial. In most models, such as spontaneous (genetic) hypertension or renal (two kidney-one clip) hypertension, no effects have been established (Rabito et al., 1981; Liard, 1984; Share and Crofton, 1984). On the other hand, rats with hereditary or surgically induced diabetes insipidus fail to develop hypertension when treated with DOCA plus salt (Friedman et al., 1960; Crofton et al., 1980; Berecek et al., 1982b) but do so when given VP treatment (Berecek et al., 1982b; Saito and Yajima, 1982).

Despite the evidence that VP plays a role in DOCA-salt hypertension, the administration of V_1 antagonists has not provided a clear-cut answer to the question of the involvement of AVP as a vasoconstrictor agent. A reduction in BP occurred in DOCA-salt hypertensive rats after the acute administration of V_1 antagonists (Crofton et al., 1979; Hofbauer et al., 1984a). However, other investigators (Rabito et al. 1981; Burnier et al., 1982; Okuno et al., 1983; Rascher et al., 1983) found no antihypertensive response in this model. It appears that the effect of V_1 antagonists depends on the method by which DOCA-salt hypertension is induced and on the degree of hypertension achieved. Furthermore, the V_1 antagonist response may be compensated for by increases in heart rate and cardiac output. If the baroreceptor reflex response is prevented by sinoaortic deafferentation, the administration of a V_1 antagonist is followed by a significant reduction in BP (Rascher et al., 1983). Using the combined antagonism of vascular and renal responses to VP, Hofbauer et al. (1984a) obtained evidence that VP contributes to the development of DOCA-salt hypertension through both vascular (V_1) and renal tubular (V_2) effects.

Other models of hypertension with increased salt consumption have been examined for VP dependency. In the early phase of hypertension, rats fed a high-sodium diet showed a significant decrease in BP response to a VP antagonist (Hinojosa and Haywood, 1984). Lee-Kwon et al. (1981) reported that a V_1 antagonist exerted only a small influence on the arterial pressure in rats with partial nephrectomy and salt hypertension. In the even more acute hypertension induced in anephric rats by the infusion of hypertonic saline, the antagonist dPTyr(Me)AVP lowered the BP significantly (Hatzinikolaou et al., 1980, 1981).

A small but significant reduction of BP was observed when a V_1 antagonist was chronically administered to rats during the development of DOCA-salt hypertension (Hofbauer et al., 1984a). The difference between treated and control rats with DOCA-salt hypertension amounted to about 15 mm Hg. This corresponds to the degree of antihypertensive effect of the same antagonist following acute administration (Hofbauer et al., 1984a).

The pressor antagonists have also been useful in studying the effects of AVP on central BP regulation. Intracerebroventricular injection, but not intravenous injection, of a V_1 antagonist blocked the pressor effects of centrally administered VP (Berecek et al., 1982a, 1984a; Unger et al., 1984). The increase in BP induced by VP administered into the locus coeruleus could also be prevented by local pretreatment with a V_1 antagonist (Berecek et al., 1984b). Furthermore, cardiovascular effects have been described following intracerebral (Matsuguchi and Schmid, 1982) and intracerebroventricular (Pittman and Lawrence, 1982) injection of VP, although extremely high doses were required. In the opinion of Rockhold et al. (1984), a central V_1 blockade can exert only a slight effect on the BP either under basal conditions or during water deprivation. They found that no effect of a V_1 antagonist on the BP could be detected following intracerebroventricular administration to water-deprived rats.

2. Coronary circulation. Although much data are available with regard to the role of VP in the general blood circulation and BP regulation, few publications can be found concerning the effects of VP on the coronary circulation. This may be due, in part, to the inherent difficulties encountered in the use of the current methodology for making direct observations concerning the changes in coronary circulation induced by VP and, especially, V_1 antagonists.

In section III.A.1 the possible mechanisms involved in the decrease in cardiac output in the different states that result in elevations of the AVP level were presented. The baroreceptor reflex appears to contribute to the lowering of the cardiac output in conscious dogs, because the decrease is greatly blunted after sinoaortic baroreceptor denervation (Montani et al., 1980). Other mechanisms also could participate in the lowering of the cardiac output by VP under normal conditions. Specifically, VP could have a negative inotropic effect, as suggested by the increased left ventricular end-diastolic pressure in conscious dogs (Heyndrickx et al., 1976). The central venous pressure generally increases by several centimeters of H_2O in conscious dogs when the plasma level increased within the physiological range (Szczepanska-Sadowska, 1973; Bie and Warberg, 1983). There is no doubt that AVP is able to decrease the coronary blood flow, but this action appears to be secondary to the

changes associated with bradycardia and a decrease in the left ventricular work associated with vagal stimulation of the heart (Heyndrickx et al., 1976). However, it seems unlikely that the negative inotropic action of VP would contribute substantially to the decrease of cardiac output or that this is a direct effect of VP, because cardiac output decreases little in barodenervated dogs.

The application of the radiolabeled microsphere technique has demonstrated substantial changes in regional vascular responses to VP. A number of observations have been described that are in reasonably good agreement, with some differences, presumably due to the various VP doses, species, and experimental conditions used (Drapanas et al., 1961; Ericsson, 1971; Heyndrickx et al., 1976; Liard et al., 1982). This type of study suggests that some vascular beds are more sensitive to the vasoconstrictor action of VP than others and that a substantial regional blood flow reduction can accompany physiological alterations of plasma VP levels. Liard et al. (1982) reported that, when the AVP level was increased by 10 pg/ml as a result of a 1-h AVP infusion into conscious dogs, the blood flow to the skin, skeletal muscle, fat, pancreas, and thyroid gland was reduced by about 30%; this reduction was proportionately greater than the decrease in cardiac output, which was decreased by 15%.

The myocardium, the gastrointestinal tract, and the brain were less sensitive to the vasoconstrictive effects of VP. In these organs, the relative blood flow reduction was similar to that of the cardiac output. Some organs (kidney and liver) did not show any decrease in their blood flow. Because the mean arterial pressure did not change during VP infusion, these flow alterations can be directly represented by the equivalent vascular resistance changes. On the other hand, Charocopos et al. (1982) found that stimulation of the release of endogenous VP with hypertonic saline in anephric rats did not induce any changes in myocardial blood flow.

In our own recent studies (László et al., 1988), the development of VP-induced coronary vasoconstriction was studied by the indirect electrocardiographic method. Because of the coronary vasoconstrictive effect, a T-wave elevation occurred which was measured in millimeters in the individual rats (fig. 4). OVP, LVP, and AVP given intravenously in doses of 2 or 4 units/kg to pentobarbital-anaesthetized rats produced a marked coronary vasoconstriction, as shown by the percentage of elevation of the T-wave. When the antagonist $d(CH_2)_5Tyr(Me)AVP$ was administered in an effective dose (184 ng/kg), a significant decrease was detected in the coronary artery spasms induced by OVP, LVP, and AVP. The V_1 antagonist completely eliminated the T-wave elevation representative of the spasm of the coronary arteries, but the bradycardia induced by VP remained unchanged.

For the study of direct effects of OVP and the V_1 antagonist, the perfusion pressure, the contractile force,

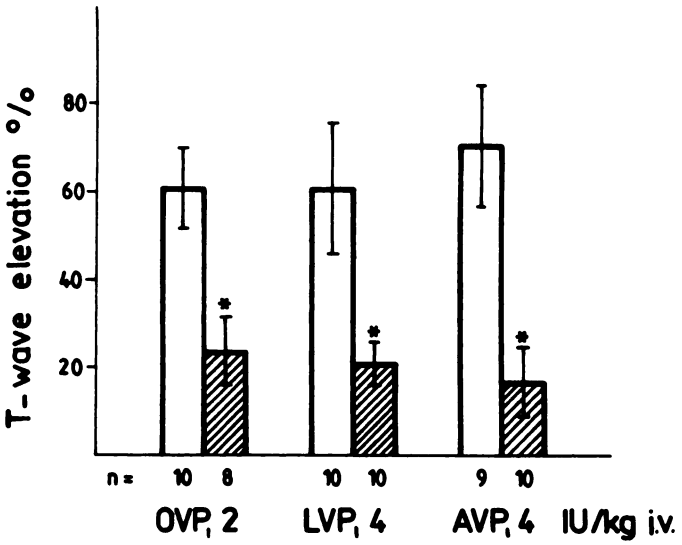

FIG. 4. Coronary vasoconstriction induced by various VP analogues alone and in the presence of V_1 antagonist. □, agonist alone; ■, agonist in the presence of $d(CH_2)_5Tyr(Me)AVP$; error bars, SEM; *, statistically significant difference (Student's *t* test; László et al., 1988).

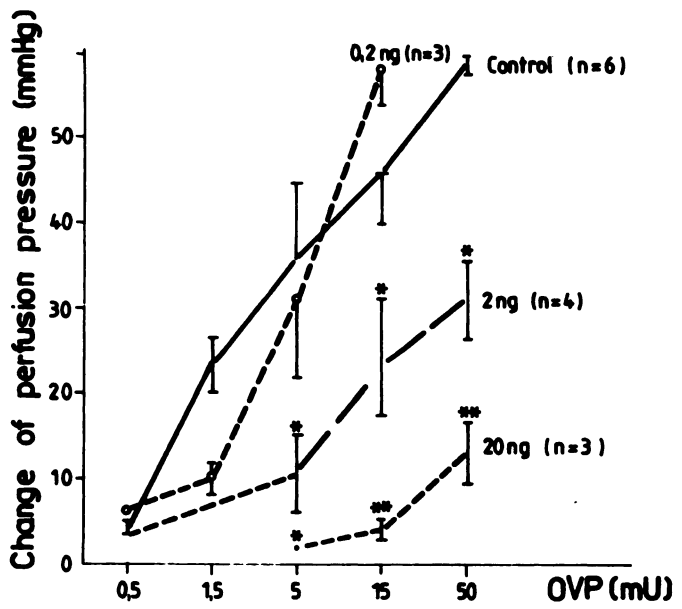

FIG. 5. Effect of V_1 antagonist on perfusion pressure changes induced by OVP in isolated heart. Error bars, SEM; *, significant difference; **, highly significant difference (Student's *t* test; László et al., 1988).

and the heart rate were measured using the isolated, perfused Langendorff heart preparation (fig. 5). Different doses of the OVP and the antagonist $d(CH_2)_5Tyr(Me)$-AVP were administered in the perfusion solution. A linear increase in the perfusion pressure was observed after OVP administration. A small dose of antagonist (0.2 ng) did not influence the change in the perfusion pressure, whereas larger doses (2.0 and 20.0 ng) significantly reduced the perfusion pressure increase induced by OVP. No substantial differences were seen in either the contractile force or the heart rate after the administration of OVP. On the basis of our results, we can

conclude that this V_1 antagonist can prevent the VP-induced coronary vasoconstriction. A similar conclusion was drawn by Kopia and Volocir, (1985).

3. Renal circulation. Study of the effects of VP on the renal haemodynamics is of great importance for two reasons: (*a*) VP influences regional circulation and, hence, the renal circulation and (*b*) the water metabolic effect of VP proceeds through the kidney. The attempts of a large number of investigators to describe the role of VP in the control of the renal haemodynamics have been frustrated by many problems. The interpretation of the experimental data is hindered by the complex interaction that exists among VP, the volume and electrolyte state, the nervous system, and other renal and extrarenal hormones. Another major problem has been the lack of a reliable experimental model. It is generally agreed that animals in which endogenous VP is excluded by sectioning the hypothalamoneurohypophyseal tract, although useful, are not ideal models. In these animals, many of the physiological parameters, e.g., the renal haemodynamics, may not be normal. To avoid this complication introduced by anaesthesia and postsurgical stress (Walker et al., 1983), trained, conscious, chronically instrumented Brattleboro rats were used in recent experiments. A great improvement was achieved by application of the Doppler technique for the direct measurement of the regional blood flow (Haywood et al., 1981; Gardiner and Bennett, 1989).

Almost 20 years ago, a new method was introduced for the measurement of the intrarenal distribution of blood flow (Ladefoged and Munck, 1971; Thurau and Levine, 1971). The uptake of ^{131}I-labeled human serum albumin was used as an index of regional perfusion in the isolated rat kidney, and the effects of AVP and OVP were studied (Cross et al., 1974). In this experimental model, the papillary perfusion decreased after the administration of AVP and OVP. However, the total renal perfusion was reduced only by the administration of high doses of hormone. A similar observation was described by Liard et al. (1982), who measured the regional blood flow with radioactive microspheres in conscious dogs during VP infusion. The renal blood vessels proved one of the most resistant regions when the regional blood flow changes were determined during the 1-h VP infusion.

VP may exert long-term effects on the renal haemodynamics, in spite of the insensitive responsiveness to the acute vasoconstrictor effect of VP. It is well known that Brattleboro homozygous rats have a lower GFR and ERPF than do Long-Evans rats (Gellai and Valtin, 1979; Gellai et al., 1984). Treatment with AVP for a few hours did not affect the renal haemodynamics, whereas prolonged administration resulted in a 50% increase in both GFR and ERPF (Gellai et al., 1983, 1984; Gellai, 1985; Valtin, 1987).

The role of VP in the control of the renal haemodynamics may be best elucidated through the use of VP antagonists. Aisenbrey et al. (1981) reported that rats deprived of water for 24 h and treated with V_1 antagonists exhibited a significant decrease in BP, as well as an increase in renal blood flow. This observation is of interest because the kidney is one of the vascular beds least sensitive to the acute vasoconstrictor action of VP, which can be due to the autoregulation of renal blood flow (Liard et al., 1982). It may suggest that the renal haemodynamic effects observed in this study are not entirely due to the blockade of the VP effects at the vascular receptors (Liard, 1985). The influence of V_1 and V_2 antagonists on the GFR and ERPF of normal Long-Evans rats was studied by Gellai et al. (1984, 1985). There was no significant change in either parameter when the antagonists were given separately. However, there was a 36% reduction in the GFR during the joint (V_1 and V_2) vascular and tubular blockade. The ERPF was not affected. Similar results were obtained in another group of rats whose ERPF was measured with an implanted Doppler flow probe.

From these results, it would seem that VP antagonists may provide us with at least partial answers. These observations of selective VP antagonists indicate that (*a*) in normally hydrated rats VP plays an important role in the control of the GFR and (*b*) the mechanism of this control involves some interaction of the vascular-glomerular and antidiuretic effects of VP.

The actions of AVP have been ascribed to two distinct cellular mechanisms, mediated by different AVP receptors (Michell et al., 1979). The vasopressor and glycogenolytic activities of AVP (V_1 receptor) are associated with an increase in cytosol-free calcium and phosphoinositide hydrolysis. Antidiuretic activities (V_2 receptor) are initiated by an increase in intracellular cAMP. It is apparent that two opposing influences of AVP on renal medullary blood flow could come into play (Kiil and Aukland, 1960; Jamison et al., 1971). A vasoconstrictor action of AVP on the vasa recta would reduce blood flow. The antidiuretic action of AVP on the collecting tubules would increase water reabsorption. The consequent increase in water uptake by these vasa recta should increase medullary blood flow. Jamison et al. (1988), using a fluorescence video-microscopic method, studied the actions of AVP and its various V_1 and V_2 receptor antagonists on medullary blood flow. The results showed that AVP reduces vasa recta blood flow both directly, by its pressor action, and indirectly, presumably by reducing the amount of water delivery to the papilla for capillary uptake. Their findings indicate that there are receptors for both the pressor (V_1) and the antidiuretic (V_2) actions of AVP in the kidney and that both mediate the effect of AVP on medullary blood flow.

From the data referred to above we can conclude that VP plays an important role in the maintenance of the BP (Cowley et al., 1974, 1980, 1981c; Laycock et al., 1979; Malayan et al., 1980; Schwartz and Reid, 1981, 1983;

Zerbe et al., 1982a). After severe bleeding or dehydration, the secretion of VP is increased (Ginsburg and Brown, 1956; Sachs et al., 1967; Chien and Usami, 1974; Aisenbrey et al., 1981; Andrews and Brenner, 1981; Schwartz and Reid, 1981, 1983). This is of importance in the correction of hypotension or the restoration of BP (Laycock et al., 1979; Altura, 1980; Cowley et al., 1980; Aisenbrey et al., 1981; Andrews and Brenner, 1981; Schwartz and Reid, 1981, 1983; Rundgren et al., 1982; Zerbe et al., 1982a, 1983; Al-Omar Azzawi and Shirley, 1984).

A similar mechanism can be presumed to be involved in the bleeding that may occur as a complication of child bearing in human beings. During pregnancy, the oestrogen level is increased, and this increases the sensitivity of the renal arteries to the vasoconstrictive effect of VP (Byrom, 1937, 1938; Byrom and Pratt, 1959; Lloyd and Pickford, 1961, 1962; Honoré, 1962a,b; László, 1981). The marked renal vasospasm is responsible for the development of renal cortical necrosis. Therefore, it is of great importance to examine how a V_1 antagonist influences the increase in BP and vascular resistance induced by VP.

The effects of VP on renal haemodynamics were studied in an experimental model of renal cortical necrosis. In previous experiments, we demonstrated that VP induced renal cortical necrosis in rats after oestrogen pretreatment (Kovács et al., 1964; László, 1981). Our observations revealed that the oestrogen sensitizes the renal arteries to the pressor effect of VP, a pronounced renal vasospasm develops, and a considerable proportion of the renal cortex undergoes necrosis as a consequence of the hypoxia (Kovács et al., 1965; Kocsis et al., 1979; László, 1981).

Histochemical and electron microscopic methods were recently applied to examine how the VP antagonist $d(CH_2)_5Tyr(Me)AVP$ influences the development of this renal cortical necrosis. The experiments revealed that VP did not induce hypoxia or necrosis in the renal tubules if the antagonist was administered simultaneously, even after oestrogen pretreatment (Kocsis et al., 1987a). Disturbance of the renal cortical circulation was convincingly proven by our haemodynamic experiments (fig. 6). The systemic BP was increased in oestrogen-pretreated rats 30 min after VP administration. A small decrease in cardiac output was detected in all VP-treated rats. One-half or 1 h after VP administration to rats pretreated with oestrogen, the renal blood flow was significantly decreased, whereas the vascular resistance was substantially increased. The V_1 antagonist prevented these changes almost completely, and the renal blood flow and vascular resistance became nearly normal after injection of the antagonist.

These results were supported by our angiographic experiments in which we localized the renal vasospasm (Kocsis et al., 1987b). After VP administration, a marked spasm occurred in the larger renal arteries, the arterio-

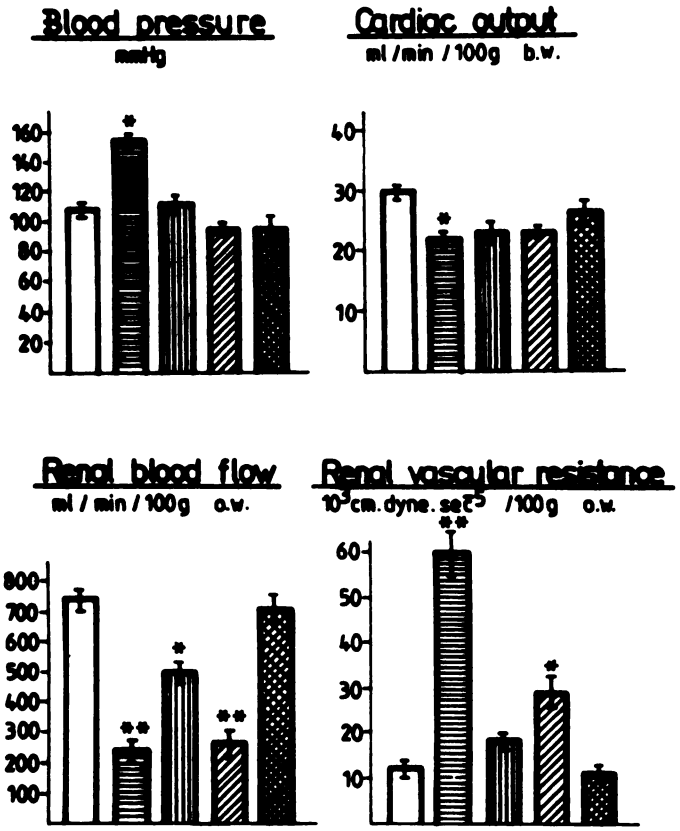

FIG. 6. Effect of V_1 antagonist on renal haemodynamic changes induced by oestrogen and VP administration. □, control (n = 15); ■, oestron + VP 0,5 h (n = 12); ■, oestrogen + V_1 antagonist + VP 0.5 h (n = 10); ■, oestrogen + VP 1 h (n = 10); ■, oestrogen + V_1 antagonist + VP 1 h (n = 10); error bars, SEM; *, significant difference; **, highly significant difference (Student's t test; László, 1981).

venous time increased, and parenchymal filling became defective. The renal circulation remained undisturbed if the V_1 antagonist was administered simultaneously. The results suggest that the VP antagonists prevent renal vasospasm after VP administration in rats pretreated with oestrogen. We conclude that treatment with the pressor antagonist may, in the future, be an important means of preventing human renal cortical necrosis.

4. Gastric circulation. Many results demonstrate a significant role of VP in the regulation of gastric circulation. According to Altura (1975), a physiological concentration of AVP (as low as 10 pg/ml) elicited a detectable vasoconstriction in the mesenteric vessels of normally hydrated rats. The arterioles exhibited a 5% decrease in lumen diameter after topical application of VP at this concentration, which represents a 20% increase in the resistance of this segment of the circulation (Altura, 1973). The vasoconstrictor responsiveness to VP appears to increase progressively as the vessel size decreases (Altura, 1970).

Charocopos et al. (1982) found that the stimulation of endogenous VP release with hypertonic saline in anephric rats led to a decrease in the blood flow to the gastrointestinal tract. This change was corrected by administration of the vasopressor antagonist

d(CH_2)$_5$Tyr(Me)AVP. In diuretic-induced volume depletion, VP appears to play a major role in the intestinal vasoconstriction that has been observed in cats (McNeill, 1974). Schmitt et al. (1981) demonstrated in dogs that VP was involved in the decrease in mesenteric conductance that results from volume loss. Earlier, Pang et al. (1979) reported that intravenous infusion of the VP antagonist deaminopenicillamine-4-valine-8-DAVP inhibited the mesenteric vasoconstrictor response to AVP in cats, but the antagonist initiated little or no vasodilation when administered alone to hypophysectomized cats.

During haemorrhage in dogs, Rocha e Silva and Rosenberg (1969) reported that VP secretion was sufficient to contribute to BP regulation. McNeill et al. (1970) found that a substantial vasoconstriction occurred in the mesenteric circulation during haemorrhage and that a normal pituitary function was needed to maintain this vasospasm. Later, Pang (1983) demonstrated that hypotension induced by haemorrhage caused significant decreases in the mean arterial pressure and cardiac output and a significant increase of the total peripheral resistance. As a result of the reductions in arterial pressure and cardiac output due to blood loss, it was expected that a reflex vasoconstriction would occur as a result of the release of various vasoconstrictor agents (VP, catecholamines, angiotensin, etc.), causing various degrees of vasoconstrictor influence in different vascular beds. They found that the relative distribution of the cardiac output to different organs was changed after haemorrhage; significant decreases in the percentage of distribution of the cardiac output were observed in the stomach and skin, small decreases in the coecum and colon, and significant increases in the liver, testes, and brain. This suggests that the vasoconstrictor influence of haemorrhage was most pronounced in the vascular bed of the stomach. d(CH_2)$_5$Tyr(Me)AVP administration significantly increased the percentage of distribution of the cardiac output to the stomach and to other organs. This shows variability in response to the VP antagonist in different vascular beds and suggests that, following haemorrhage, endogenously released VP contributed significantly to the maintenance of the arterial pressure and blood flow distribution and exerted a considerable vasoconstrictive influence in vascular beds of different organs. In this respect, the question arises of whether or not the vasoconstriction obtained is beneficial.

Errington and Rocha e Silva (1974) showed that, following severe haemorrhage, dogs died with typical lesions of haemorrhagic shock. In contrast, dogs with surgically induced VP deficiency survived. It was concluded that a less pronounced mesenteric vasoconstriction occurred in the absence of VP, with less ischaemic anoxia of the intestines as a consequence. On the other hand, Altura (1980) reported that rats with diabetes insipidus are extremely sensitive to haemorrhagic shock and also to bowel ischaemic shock.

We recently studied the effects of VP and its antagonist on the gastric circulation (László et al., 1990). It is known that physiological doses of VP cause vasoconstriction in the intestinal tract (Liard et al., 1982). High doses of VP produced a significant vasospasm in the stomach, with mucosal damage secondary to ischaemia (Ritchie, 1975). Gastric mucosal injury develops in a haemorrhagic shock model (Kivilaakso et al., 1978; Moody et al., 1978; Leung et al., 1985). VP apparently plays an essential role in generating mesenteric vasoconstriction following haemorrhage (McNeill et al., 1970; Stark et al., 1971). The presence of VP receptors in the mesenteric vascular beds suggests its pathophysiological importance (St.-Louis and Schiffrin, 1984). These data prompted us to study the role of VP in gastric cytoprotection, which means the prevention of chemically induced (ethanol, HCl, NaOH) haemorrhagic gastric erosions without inhibition of acid secretion (Robert, 1979; Silen, 1988; Robert et al., 1989). The number of gastroprotective agents is steadily increasing (somatostatin, prostaglandin, sulphydryl, etc.), but how they act is not fully understood. The presence or absence of vascular endothelial damage and increased vascular permeability are well-known controlling factors in gastric mucosal injury or protection (Leung et al., 1985; Szabo et al., 1985).

First, we analysed how VP deficiency influences gastric mucosal injury. A dose of 1 ml of 75% ethanol was administered through a gastric tube into the stomach of intact female Brattleboro rats (basic study) and after the pretreatment with LVP (a V_1 and V_2 agonist) or dDAVP (a selective V_2 agonist). One hour later, the rats were killed, and the stomach was removed after laparatomy, dissected along the greater curvature, stretched out, and photographed. The areas of the eroded parts (petechiae, haemorrhagic streaks, confluent haemorrhage) and the total mucosa were determined planimetrically, and the ratio of the two was calculated and expressed as a percentage. The degree of the cytoprotection was calculated according to the protective index formula: $100\ [1 - (x/x_c)] \pm 100\ (SEM/x_c)$, where x = the average total area of the lesions in the treated rats and x_c = the corresponding area in the control group. A positive value meant protection; a negative one meant aggravation of the extent of the lesions compared to the controls.

In the basic study (fig. 7), the rats received ethanol alone. The degree of protection was 80% in the homozygous Brattleboro rats, compared with very low levels in the Wistar and heterozygous rats. The same type of rats were treated with LVP or dDAVP before ethanol administration. The gastric lesions were significantly more extensive in LVP-pretreated Wistar and Brattleboro heterozygous rats. The Brattleboro homozygous rats displayed the basic control findings of gastric haemorrhage. dDAVP caused no change in the basic situation.

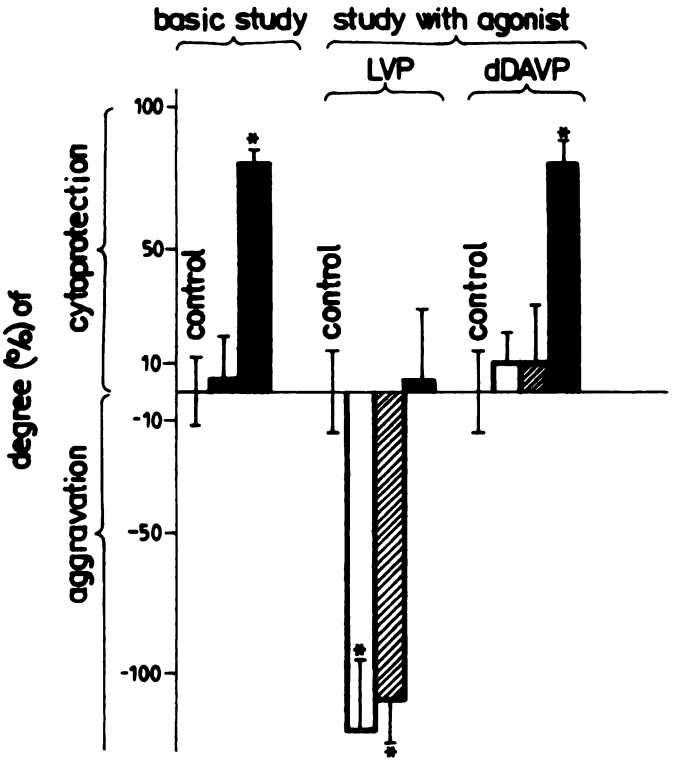

FIG. 7. The role of VP in gastric cytoprotection. □, Wistar rats (n = 10); ■, Brattleboro heterozygous rats (n = 10); ■, Brattleboro homozygous rats (n = 10); error bars, SEM; *, significant difference; **, highly significant difference (Student's t test; László et al., 1991).

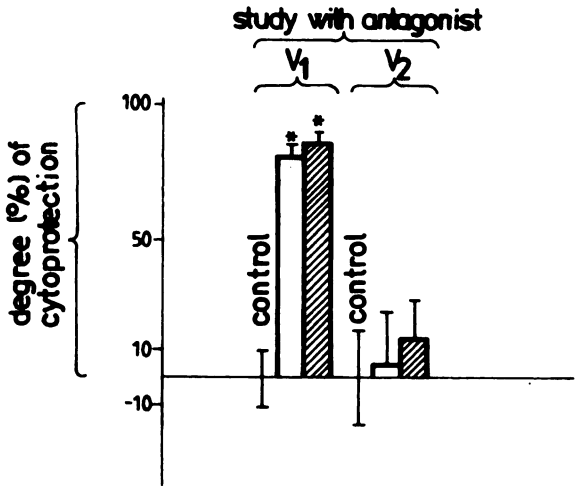

FIG. 8. V_1 antagonist protects the rat gastric mucosa against 75% ethanol-induced injury. □, Wistar rats (n = 10); ■, Brattleboro heterozygous rats (n = 10); error bars, SEM; *, significant difference; (Student's t test; László et al., 1991).

Later, we studied the effect of the V_1 antagonist $d(CH_2)_5Tyr(Me)AVP$ and the V_2 antagonist $d(CH_2)_5$ D-Ile^2,Ile^4AVP on the development of ethanol-induced gastric lesions. The results are shown in fig. 8. The V_1 antagonist was found to be gastroprotective in Wistar and Brattleboro heterozygous rats, whereas the V_2 antagonist had no effect in our model. Finally, we studied (László et al., 1989) a possible connection between the rates of development of the mucosal lesions and the plasma VP levels, while the blood ethanol content was measured in parallel (fig. 9). The gastric lesions appeared in the first minute and were completed at 30 min. The blood ethanol reached the maximum level at 15 min and then decreased slightly. The AVP plasma concentration started to increase at 15 min, attained the maximum at 30 min, and maintained this level up to 60 min. It is well known that ethanol suppresses the release of VP and causes diuresis generally, but in ethanol-intoxicated states the opposite has been observed in humans: the plasma VP concentration increased significantly if the volunteers consumed a high dose of ethanol (Linkola et al., 1978). In our experiments, the same phenomenon was detected.

In conclusion, endogenous VP had been found to play an important role in the pathomechanism of ethanol-induced gastric haemorrhagic erosions. A VP deficiency and the V_1 antagonist exerted similar gastric protection during the mucosal microcirculatory disturbance due to the vasospasm caused by VP. V_1 antagonists may offer new perspectives in the treatment of peptic ulcer disease.

B. Role of V_2 Antagonists in Water Metabolism

1. Effects of V_2 antagonists on the antidiuretic action. The recent discovery and characterization of competitive VP antagonists have provided new tools with which to probe the scope and diversity of antidiuretic mechanisms. In this respect, the most important problem is that no selective V_2 antagonists are available; all V_2 antagonists have a V_1 antagonist effect as well. Some V_2 antagonists such as $d(CH_2)_5Tyr(Et)$ VAVP, also display V_2 agonistic activity. In the discussion of the results relating to V_2 antagonist studies, we drew attention to these problems (section II.D).

These antagonists are capable of blocking the antidiuretic effects of exogenous AVP (Sawyer et al., 1981b; Ishikawa et al., 1983; László et al., 1984a,c; Schrier and Kim, 1984). The V_2 antagonist $d(CH_2)_5Tyr(Et)$ VAVP decreases the antidiuretic action of exogenous VP in Brattleboro homozygous rats (fig. 10). AVP decreases the urinary output in a dose-dependent manner. The administration of the V_2 antagonist before the AVP injection moderated the diuresis inhibition considerably. Acute administration of this compound to dehydrated or normally hydrated rats induced a marked increase in the urine volume and a reduction in the urine osmolality (fig. 11). The maximum level of polyuria occurred in the second hour. In this period, the quantity of urine attained the level typical for homozygous Brattleboro rats. The diuretic action of the antagonist is temporary; after 4 h the urinary osmolality returned to the normal level. The urinary osmolality varies accordingly. It is decreased by a V_2 antagonist in a dose-dependent way. On the other hand, it has been reported that an acute V_2 receptor blockade had no effect in water-loaded rats or in rats with VP deficiency (Kinter et al., 1984a,b; Mah et al., 1986).

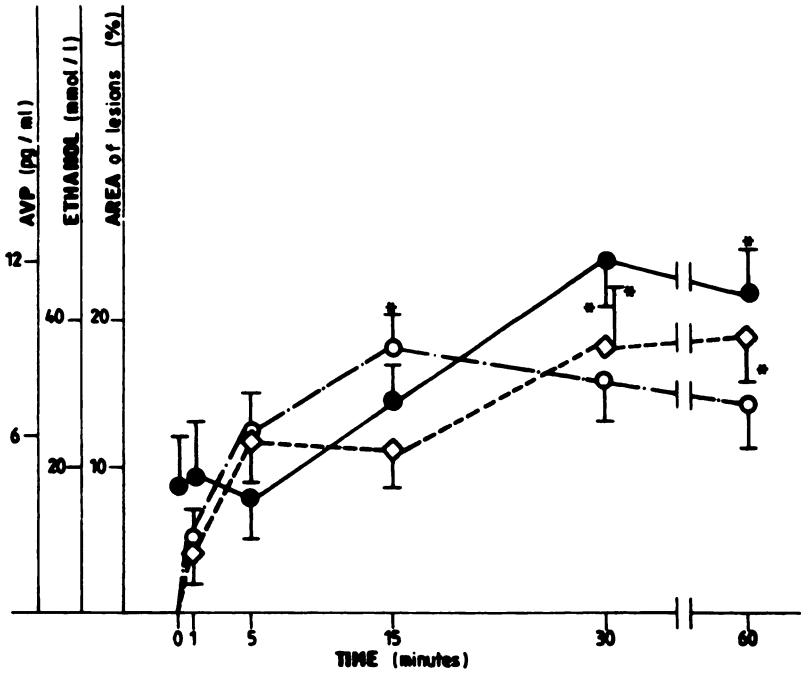

FIG. 9. A time relation study of plasma AVP, blood ethanol, and the territory of 75% ethanol-induced gastric lesions in rats ($n = 10$). ◇, area of lesions; ○, ethanol level; ●, plasma AVP level; error bars, SEM; *, significant difference; (Student's t test; László et al., 1989).

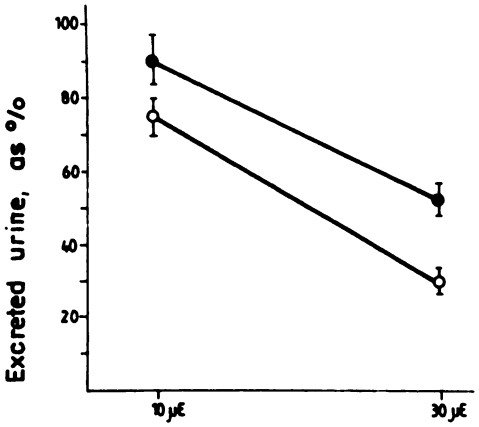

FIG. 10. Percentage of change in urine excretion in response to VP antagonist ($n = 10$). ○, AVP; ●, AVP +V_2 antagonist; error bars, SEM (László et al., 1984a).

Chronic administration of the V_2 antagonist d(CH_2)$_5$D-Tyr(Et)VAVP to normal Sprague-Dawley rats induced an increase in urine output and a decrease in urine osmolality on the first day of treatment (Hofbauer et al., 1985). The water intake increased significantly to values similar to those observed in Brattleboro rats. However, during the following days the water intake progressively decreased and it normalized by the end of 1 wk. The mechanisms causing the normalization of water balance during a continuous V_2 blockade are not clearly explained, but an agonistic effect of the antagonist might be involved (Hofbauer et al., 1985). The agonistic effects may be more easily detected in rats lacking endogenous AVP. Hofbauer et al. (1985) demonstrated an intrinsic antidiuretic activity of this compound when it was infused for several days in Brattleboro homozygous rats. In these experiments, the antagonist normalized the water intake to the same degree as did exogenous VP. This effect persisted throughout the period of administration and for several days after the treatment had been stopped. A partial agonist action also was supported by other research groups (Vilhardt and Lundin, 1987; Kinter et al., 1988; Mah et al., 1988).

Recently, Szczepanska-Sadowska et al. (1987) studied the effects of the central administration of a V_2 antagonist to investigate how it influences thirst. Observations of the osmotic thirst threshold, the osmotic load excretion, and postloading restitution of the plasma osmolality were made in dogs, both in control experiments and during the infusion of V_2 antagonists into the third ventricle. A significant elevation of the osmotic thirst threshold could be elicited by the administration of various V_2 antagonists. This treatment was associated with a significant suppression of the postloading water intake and osmotic load excretion and with a delay in restitution of the plasma osmolality. These observations indicate that centrally released VP may participate in the control of thirst and that this central effect of VP can be blocked by V_2 antagonists.

It is well known that a higher AVP plasma level has been implicated in impaired water excretion in adrenal insufficiency (Schrier and Bichet, 1981; Laczi et al., 1987). Acute treatment with a V_2 antagonist improved the ability of mineralo- or glucocorticoid-deficient rats to excrete a water load (Ishikawa and Schrier, 1982, 1984). This indicates that the impairment of their renal diluting capacity was at least partly a consequence of the increased plasma AVP level. The impaired water excre-

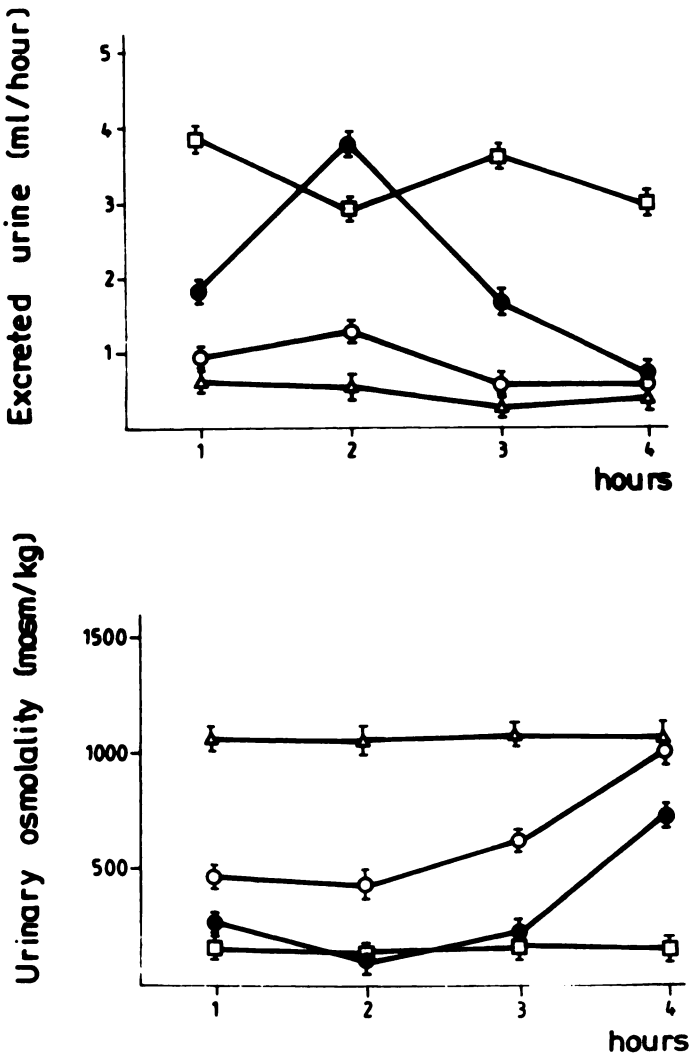

FIG. 11. Effect of V_2 antagonist on urine excretion and osmolality ($n = 10$). Δ, physiological NaCl; ○, 10 μg/kg antagonist; ●, 30 μg/kg antagonist; □, Brattleboro homozygous untreated rats; error bars, SEM (László et al., 1984a).

tion of rats with inferior vena cava constriction was completely normalized following the administration of a V_2 antagonist (Ishikawa et al., 1986). In DOCA-salt hypertensive rats, the acute administration of a V_2 antagonist increased the urinary output but did not decrease BP any more strongly than did a V_1 antagonist (Hofbauer and Mah, 1987).

These observations suggest that the antihypertensive effects of the V_2 antagonist were entirely attributable to the V_1 receptor blockade. On the other hand, chronic treatment with a V_2 antagonist almost completely prevented any increase in BP during the development of DOCA-salt hypertension (Hofbauer et al., 1984a). After 1 month of treatment the BP in rats receiving the V_2 antagonist was approximately 40 mm Hg lower than that in DOCA-salt hypertensive rats without antagonist and 25 mm Hg lower than that in rats treated with a selective V_1 antagonist. These observations suggest that VP contributes to the development of DOCA-salt hypertension, not only through its vascular effect but also through its renal tubular (aquaretic) effect. However, rats treated with a V_2 antagonist developed severe hypernatriaemia and exhibited a poor general condition, which might have resulted in a nonspecific lowering of the BP (Hofbauer et al., 1984a).

2. Prevention of hyponatriaemia and cerebral oedema by V_2 antagonists. Whereas the primary effect of VP antagonists is to increase the free water clearance, increases in renal solute excretion have been reported. In rats, all aquaretic (V_2) antagonists tested by Kinter et al. (1984a, 1986) were associated with modest, but statistically significant, increases in renal sodium excretion. The excretion rates associated with V_2 antagonist administration exceeded those associated with similar changes in urine flow rates stimulated by water loading (Kinter et al., 1985, 1987). It is possible that the increase in electrolyte excretion reflects antagonist inhibition of VP-dependent salt reabsorption. However, this effect of the V_2 antagonist has a species specificity. No increases in renal electrolyte excretion were observed in association with the administration of V_2 antagonists in dogs (Kinter et al., 1984b) or squirrel monkeys (Kinter et al., 1985, 1986). In accordance with this observation, a severe hypernatriaemia developed after the chronic administration of V_2 antagonists (Hofbauer et al., 1985).

The role of VP in SIADH is well established (Kinter et al., 1985). The syndrome was first described by Schwartz et al. (1957) in connection with bronchial carcinoma. The presence of elevated levels of VP has now been reported in hyponatriaemic patients (Anderson et al., 1985) and has been confirmed by others (Gross et al., 1986, 1987). Ever increasing significance is attributed to SIADH, which involves water retention, hypernatriuria, hyponatriaemia, and cerebral oedema (Edwards, 1977). The diagnosis of SIADH does not generally cause difficulty but adequate treatment of the syndrome is a problem that has not yet been solved.

A rat model of SIADH was created by the administration of a high dose of a long-acting VP preparation (pitressin tannate) together with forced water intake (László et al., 1984b). Without hydration to substitute for the daily water consumption, even a high dose of VP preparation does not give rise to water intoxication, which is the essence of SIADH (László and Baláspiri, 1986). We have investigated whether the V_2 antagonist $d(CH_2)_5Tyr(Et)VAVP$ can prevent water intoxication (László et al., 1984b).

Considerable water retention can be observed following the administration of a large dose of posterior pituitary hormone (fig. 12). When the antagonist was simultaneously administered, water retention could be prevented. The osmolality of the urine of pitressin-treated animals was increased 3-fold on the first day after treatment and decreased the mean level of the control on the

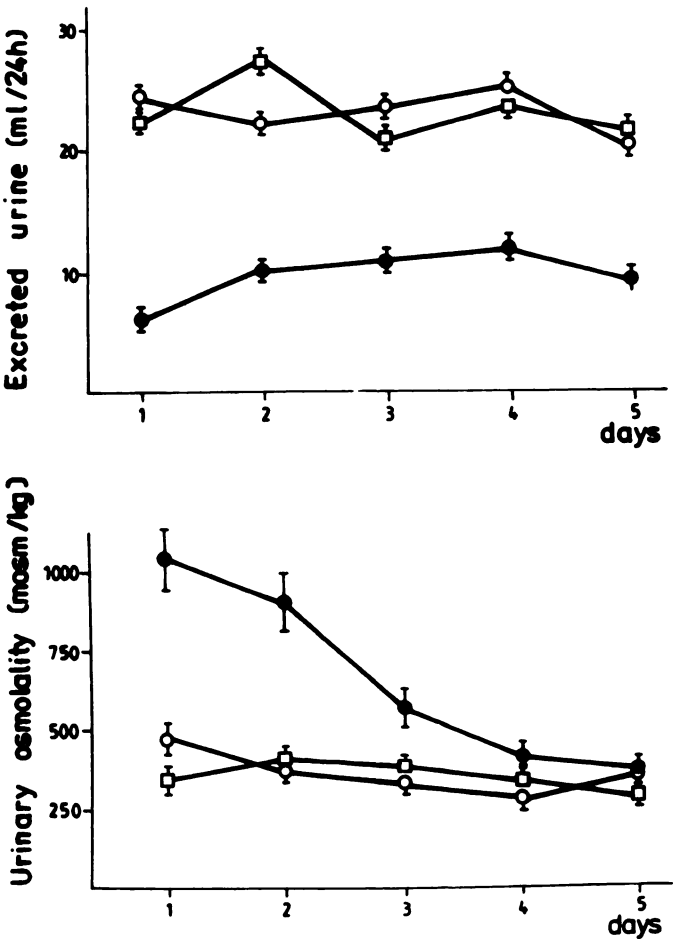

FIG. 12. Effect of V_2 antagonist on urine excretion and osmolality of rats treated with pitressin (n = 10). ○, untreated; ●, pitressin; □, pitressin + antagonist; error bars, SEM (László et al., 1984b).

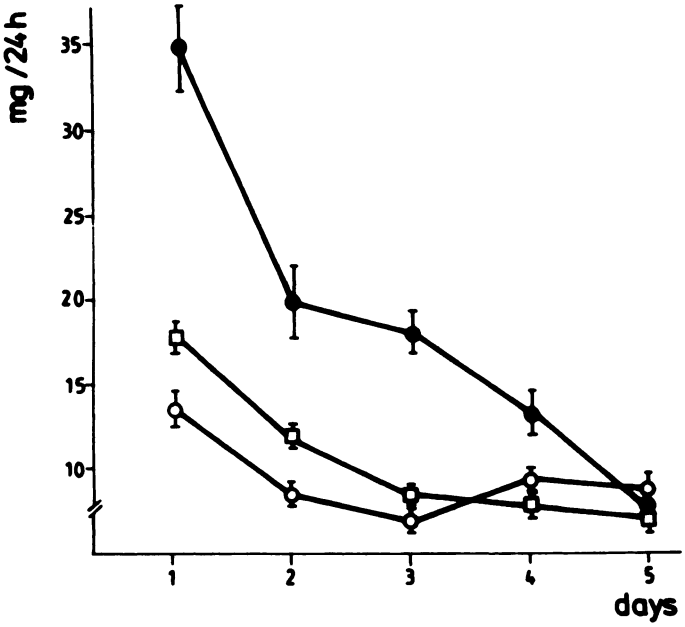

FIG. 13. Effect of V_2 antagonist on sodium excretion of rats treated with pitressin (n = 10). ○, untreated; ●, pitressin; □, pitressin + antagonist; error bars, SEM (László et al., 1984b).

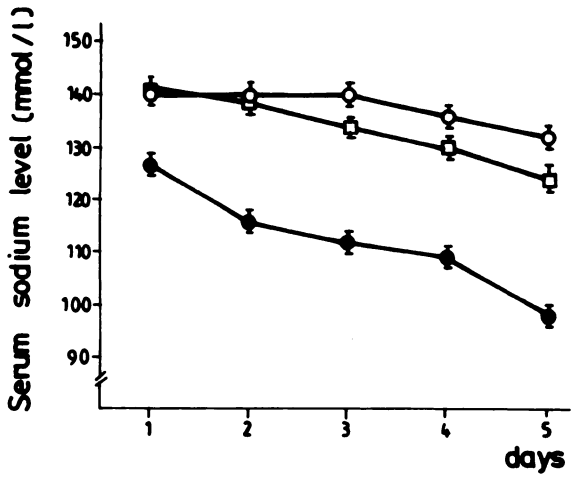

FIG. 14. Effect of V_2 antagonist on serum sodium level of rats treated with pitressin (n = 10). ○, untreated; ●, pitressin; □, pitressin + antagonist; error bars, SEM (László et al., 1984b).

fourth to fifth day of the therapy. The V_2 antagonist abolished the change in the urinary osmolality.

In response to pitressin administration, the sodium excretion (fig. 13) increased considerably on the first day after treatment and subsequently decreased progressively, reaching the control levels on the fifth day. The antagonist substantially moderated the elevated natriuresis. Corresponding changes were observed in the serum sodium level (fig. 14). In response to the VP preparation (with forced hydration), the serum sodium level started to decrease on the first day of treatment. The hyponatriaemia later became more marked, the sodium levels declining to <100 mmol/liter by the end of the experimental period. One-third of the animals died within 5 days of treatment.

In rats that received V_2 antagonist together with pitressin, only a moderate decrease in the serum sodium level was found; this occurred on the third to fifth days of treatment. These animals tolerated the treatment well. At the end of the experimental period, the serum osmolality and cerebral water content were determined (table 3). In pitressin-treated rats, the serum osmolality was decreased significantly, whereas the weight of the brain was higher because of its increased water content. By means of administration of a V_2 antagonist, these changes could be prevented completely. A similar observation was reported by Dytko and Kinter (1986).

We induced water intoxication in rats in the same manner by administering a high dose of dDAVP instead of pitressin (László and Baláspiri, 1986). The treatment led to water retention, hypernatriuria, hyponatriaemia, and severe cerebral oedema. These alterations could be prevented by the simultaneous administration of $d(CH_2)_5Tyr(Et)VAVP$. Additionally, established hyponatriaemia was corrected following the acute administration of as little as 20 μg/kg of $d(CH_2)_5DTyr^2(Et)$-$Val^4desGly^9AVP$ to conscious rats. These observations seem rather important in human cases because the use of dDAVP is so widespread in the treatment of diabetes

TABLE 3

Effect of vasopressin antagonist on serum osmolality and water content of brain in rats treated with pitressin

Groups	No. of animals	Body weight (g)	Blood pressure (mm Hg)	Serum osmolality (mOsm/kg)	Weight of brain (g)	Water content of brain (mg/100 mg wet weight)
1 Untreated	10	180.7 ± 7.1*	117.5 ± 7.3	285.0 ± 20.7	1.56 ± 0.11	75.0 ± 1.1
2 Pitressin	10	198.2 ± 12.3	115.5 ± 4.5	236.2 ± 11.3†	1.87 ± 0.13†	78.1 ± 0.6†
3 Pitressin + antagonist	10	187.0 ± 10.6	122.5 ± 5.1	275.4 ± 16.9	1.57 ± 0.10	74.5 ± 1.3

* Mean ± SEM.

† $P < 0.05$ compared with untreated rats (Student's t test).

insipidus and urinary incontinence. The correction of experimental hyponatriaemia with the VP antagonist is rapid and predictable, as compared with the slow onset and associated risks of demeclocycline (Forrest et al., 1978; Kinter et al., 1985) and the potentially unpredictable nature and risks of hypertonic saline (Ayus et al., 1985a,b).

The role of central VP in the regulation of brain water content is now under investigation in several laboratories; VP has been implicated in the pathogenesis of experimental brain oedema (Doczi et al., 1984; László et al., 1984b; László and Baláspiri, 1986; Reeder et al., 1986) and a central V_2 receptor mechanism has been postulated (Rosenberg et al., 1986). Central administration of a V_2 antagonist has been reported to attenuate vasogenic brain oedema in cats (Weinand et al., 1990). In rats with ischaemia of the forebrain resulting from occlusion of both common carotid arteries for 4 h, the observed increases in brain water were significantly reversed by the injection of the V_2 antagonist $d(CH_2)_5$D-Ile^{2}Ile^{4}AVP (Tang and Ho, 1988). Doczi et al. (1990) reported that significant cerebral oedema induced in rats by artificial cerebral bleeding was significantly reduced by the same V_2 antagonist, suggesting a new approach to the treatment of cerebral oedema.

C. Role of Vasopressin Antagonists in the Release of Adrenocorticotrophic Hormone

The first demonstration of the existence of CRF was reported by Saffran and Schally (1955), and then by Guillemin (1955). It was initially suggested that VP was identical with CRF (Martini and Morpurgo, 1955; McCann, 1957). There was good evidence for this view, because stress causes the release of both VP and ACTH, the median eminence is in close contact with nerves of the supraopticohypophyseal tract, and neurosecretory substances have been observed to enter the pituitary portal vessels. This hypothesis was strengthened by the observations that the VP enhances adrenocortical activity in normal, but not hypophysectomized, rats (De Wied, 1961) and that some responses to neurogenic stress were decreased after removal of the neurohypophysis (Smelik et al., 1962).

The participation of VP in the secretion of ACTH in the rat has been extensively studied. VP releases ACTH from cultured pituitary cells or pharmacologically blocked (treated with Nembutal, morphine, and dexamethasone) rats but exhibits a lower potency and intrinsic activity than does CRF itself (Vale and Rivier, 1977; Aizawa et al., 1982; Rivier and Vale, 1983a; Vale et al., 1983). The stimulatory effect of VP was recognized long after the establishment of the pressor and antidiuretic effects of VP. Given this temporal sequence of discoveries, it is not surprising that there have been a number of attempts to relate the more recently discovered effects to the classic effects on vascular beds and renal tubules. This has most often been done by comparing the potencies of VP and a number of its analogues in eliciting various effects.

These studies span a period of 20 years and both in vivo and in vitro approaches were used, but almost always rats were used. Some of these reports, in vitro (Pearlmutter et al., 1974) and in vivo (De Wied et al., 1951; Aizawa et al., 1982; László et al., 1983), suggest that the ACTH-releasing potency of VP and its analogues is correlated with pressor activity. However, other studies (Doepfner et al., 1963; Arimura et al., 1969; Knepel et al., 1984a), including one that was carried out in humans (Andersson et al., 1972), failed to show such a correlation. Certainly, it is possible that a given series of analogues might demonstrate a positive correlation between these two variables, and another series might not. Thus, the safest categorical conclusion is that these two types of effects are not related (Jones and Gillham, 1988).

This is the same conclusion as that drawn from comparisons of ACTH-releasing and antidiuretic activity. This time virtually complete agreement exists among the publications from different laboratories (Arimura et al., 1969; Andersson et al., 1972; Aizawa et al., 1982; Knepel et al., 1984a) that the potency of VP analogues in relationship to other members of pro-opiomelanocortin (β-lipotropin, β-endorphin) is also quite independent of the pressor or antidiuretic potencies. Knepel et al. (1984b) studied the CRF-41 potentiating effect of VP analogues and found that (if only the ACTH-releasing effect was considered) there was no correlation with either pressor or antidiuretic effects.

To resolve this issue, specific VP antisera and VP antagonists were used to block the CRF-like activity of VP. Carlson et al. (1982) reported that the ACTH release evoked by electrical stimulation of the paraventricular nucleus can be inhibited by the intracerebroventricular

administration of VP antiserum. In similar experiments, Carlson and Gann (1984) demonstrated that the intracerebroventricular administration of VP antiserum inhibited the ACTH response to the stress of haemorrhage, but only in dexamethasone-pretreated rats. The inhibition of stress-induced ACTH secretion by passive immunization has also been examined by Linton et al. (1985). In this experimental series, an antiserum against LVP or CRF-41 was administered systematically. The ACTH responses to restraint or formalin stress were greatly decreased by the CRF-41 antiserum and, to a lesser extent, by the VP antiserum.

The same rationale has been applied in studies in which VP antagonists were administered instead of antisera. When V_1 antagonists were tested for their ability to decrease stress-induced ACTH secretion, Rivier and Vale (1983b) showed that such antagonists will inhibit the ACTH response in ether-stressed rats, but only in the later phase of the response (after 10 min). On the other hand, Morméde (1983) found that the same antagonists failed to inhibit the ACTH release in response to a novel environment, even though it did block the ACTH response to exogenous VP. He suggested that these results may argue against physiological significance for VP in stress-induced ACTH secretion, but he also recognized the possibility that extrahypophyseal effects of VP may be involved. The latter consideration has been supported by the findings of Baertschi et al. (1984), who showed that V_1 antagonists do not inhibit the direct pituitary stimulation of ACTH by VP in vitro. This observation also revealed that, even though the antagonists did not reduce the ACTH stimulatory effect of VP, they did inhibit its CRF-potentiating effect in pituitary cultures. This would imply some influence on V_1 receptors, specifically in the CRF-potentiating effect of VP, and would be in agreement with the results of the extensive examinations of this hypothesis by Rivier et al. (1984). These workers studied the effects of V_1 and V_2 antagonists and found that the former, but not the latter, very significantly decreased both the ACTH stimulation and the CRF response to VP. On the basis of experiments with VP antiserum and VP antagonists, there is good reason to believe that endogenous VP is involved both in the stimulation of ACTH secretion and in the potentiation of the effect of CRF.

These results have been utilized to answer the question of whether VP is physiologically involved in the regulation of ACTH secretion. In this case, the answer is definitely positive. The physiological role of VP in controlling ACTH secretion has been supported by experiments showing that the administration of VP antagonists decrease the plasma ACTH concentration in ether-stressed rats (Rivier and Vale, 1983b). These authors described, in agreement with previous publications (Arimura et al., 1967; Wiley et al., 1974), the significantly lower ACTH response to stress seen in homozygous Brattleboro rats.

Because the ability of a large dose of CRF to stimulate ACTH release was comparable in both homozygous and heterozygous Brattleboro rats (thereby suggesting that the pituitary responsiveness to CRF was not significantly impaired in animals with VP deficiency), it seems reasonable to hypothesize that the absence of synergism between VP and CRF in homozygous rats was responsible in part for their diminished pituitary secretion during stress (McCann et al., 1966; Wiley et al., 1974; Gillies and Lowry, 1980; Linton et al., 1983). These observations suggest that VP plays a significant role in regulating the response of the pituitary-adrenal axis to stress and that, as previously demonstrated, VP interacts with CRF to control ACTH release (Portanova and Sayers, 1973; Yates et al., 1974; Gillies and Lowry, 1979; Beny and Baertschi, 1982; Gillies et al., 1982; Turkelson et al., 1982; Rivier and Vale, 1983b; Vale et al., 1983; Knepel et al., 1984b).

The importance of the interaction between VP and CRF in promoting ACTH secretion has been studied in several laboratories. It is known that VP markedly potentiates the action of CRF to increase ACTH secretion both in vitro (Beny and Baertschi, 1982; Giguere and Labrie, 1982; Gillies et al., 1982; Turkelson et al., 1982; Rivier and Vale 1983b; Vale et al., 1983; Knepel et al., 1984b) and in vivo (Rivier and Vale, 1983a), and it has been suggested that the strong stimulatory action of VP in elevating the plasma ACTH level in conscious rats necessitates the presence of circulating levels of CRF. This is supported by the weak activity of VP in pharmacologically blocked rats or in rats whose endogenous CRF had been neutralized by immunological means. However, large doses of the VP agonist dDAVP appear to increase ACTH secretion through its ability to potentiate CRF (Rivier and Vale, 1985). These results strongly support the hypothesis that CRF is necessary for the maximal effect of VP on ACTH release.

The involvement of the pituitary receptors in the stimulatory action of VP on the corticotrophs is still controversial. Because the peripheral effects of VP on the circulatory system and water metabolism are mediated through V_1 and V_2 receptors, respectively (Jard, 1981), a number of investigators have attempted to determine whether the pituitary receptors responsible for the effects of VP at the hypophyseal level are related to either V_1-like (pressor) or V_2-like (antidiuretic) receptors. However, as illustrated by the results presented by Rivier and Vale (1985), the usefulness of VP antagonists in studies that seek information concerning the nature of the pituitary receptors for VP is somewhat restricted by the complex effects of analogues that exhibit both inhibitory and stimulatory effects on ACTH secretion. Using these analogues, several in vitro studies have been directed at the characterization of pituitary VP receptors

because, in the experiments in vivo, it could not be ascertained whether the ACTH and β-endorphin-releasing activities of the analogues were due to a direct effect of the pituitary. The observations made by Knepel et al. (1983, 1984a,b, 1986) and other researchers (Antoni, 1984; Antoni et al., 1984; Baertschi and Friedli, 1985) suggest that the structural requirements of the anterior pituitary VP receptor may be different from those of both V_1 and V_2 receptors.

D. Characterization of Vasopressin Receptor Subtypes with Antagonists

It is generally known that pharmacological regulation of water metabolism is affected by the diuretics that increase not only water excretion but also salt excretion. Because water reabsorption in the kidney is uniquely regulated by VP, blockade of the antidiuretic activity of VP could enhance water excretion specifically. Action of VP antagonists in the human nephron suggests important therapeutic implications for specific treatment of the different pathological states of water retention. In recent studies of isolated human medullary and papillary collecting tubules, the VP antagonist completely inhibited the stimulation of adenylate cyclase by VP (Kim and Schrier, 1985). Similar results have been reported in the dog (Kinter et al., 1984b), the rat (Stassen et al., 1985), and the monkey (Stassen et al., 1985).

The mechanism of VP action on the target organ has been studied by different methods. The most convenient tissue was kidney as a target of an aquaretic agent. The affinity of compounds for the receptor could be determined directly via radioligand-binding competition (Bockaert et al., 1973), and agonism and antagonism could be measured in vitro because the second messenger is known to be cyclic AMP (Orloff and Handler, 1962; Anderson and Brown, 1963; Brown et al., 1963; Grantham and Burg, 1966; Morel et al., 1978). When the rank order of inhibitory potency of VP analogues on the VP-stimulated membrane adenylate cyclase in rat and monkey kidney was compared with the rank order of inhibitory potency on VP-induced contraction of rat aortic rings, and VP-induced aquaretic activity, a correlation was found with blockade of the renal VP receptor and not with antipressor activity.

These findings support the hypothesis that potent antagonists of renal VP receptors in vitro can induce aquaresis in vivo. This mechanism does not apply to all VP-sensitive tissues. In particular, it was shown that VP stimulates glycogenolysis in isolated hepatocytes without affecting intracellular cyclic AMP levels. At the same time experimental data have accumulated to indicate that an increase in cytosolic free calcium plays an important role in the glycogenolytic responses to VP (Khoo and Steinberg, 1975; Shimazu and Amakawa, 1975; Stubbs et al., 1976; Keppens et al., 1977; Vandenheede et al., 1977; Van de Werve et al., 1977; Hems et al., 1978; Keppens and De Wulf, 1979b). It is clear, therefore, that different VP receptor subtypes can be distinguished on the basis of functional studies.

Michell et al. (1979) proposed the distinction of two subtypes of VP receptors. On the basis of their experiments on hepatocytes, the authors concluded, "The studies on isolated hepatocytes and upon renal membrane by Hechter et al. (1978) suggest that there are at least two distinct populations of VP receptors and that they are functionally equivalent to previously known pairs of receptors responsive to single ligands. In the hepatocyte, VP interacts with a receptor population which controls the cells by bringing about a rise in cytosolic Ca^{2+} concentration (Blackmore et al., 1978) and which also stimulates phosphatidyl-inositol breakdown. Functionally, this receptor is analogous to the α-adrenergic receptor (Jones and Michell, 1978) and to the H_1-histamine receptor (Jafferji and Michell, 1976), and it would, therefore, seem appropriate to name it V_1-vasopressin receptor. By contrast, renal VP receptors control adenylate cyclase and are, therefore, functionally analogous to β-adrenergic receptors and H_2-histamine receptors, and we would propose that these should be named V_2-vasopressin receptors."

This terminology is now widely accepted, although with a slightly different meaning, V_2 being applied to the receptors responsible for the antidiuretic effect of VP and V_1 for the receptors responsible for the vasopressor action.

In the course of the past decade, the systematic analysis of successive sites along the nephron where the VP may regulate the cell function by stimulating the intracellular production of cAMP revealed unexpected findings and thereby raised a series of new questions. The development of a micromethod designed to measure the hormone-dependent adenylate cyclase activity in single and well-localized pieces of tubules (Imbert et al., 1975) made it possible to investigate the sites along the nephron where VP exerts physiological effects via the intracellular production of cAMP as second messenger. Morel et al. (1987) reported that VP might exert effects via V_2 receptors coupled to cAMP generation, not only in the cells of cortical and medullary collecting tubules but also in other epithelial cell types of the nephron, such as those in the thin ascending limb, the medullary and cortical portions of the thick ascending limb, and the early distal convoluted tubule.

It is necessary to mention that other hormones have also been observed to stimulate adenylate cyclase in some of these segments. The enzyme present in the rat thick ascending limb responded to parathyroid hormone, glucagon, calcitonin (Bailly et al., 1980; Torikai et al., 1981; Morel et al., 1982; Imbert-Teboul et al., 1984), and, to a lesser extent β-adrenergic agonists (Morel et al., 1979) and VP (Morel et al., 1987). These observations confirm that these different hormones stimulate a common pool of adenylate cyclase in the cortical and medullary thick

ascending limbs. Consequently, they should elicit the same biological effects in these structures (Morel et al., 1982, 1987). There is evidence that the V_2 receptors might also be expressed in pig seminal vesicles (Maggi et al., 1987). VP was shown to inhibit the adenylate cyclase present in the particulate fraction from human blood platelets when incubated in the presence of guanosine triphosphate and NaCl (Vanderwel et al., 1983).

Abramow et al. (1987) described the main events involved in the increased production of cAMP with physiological and/or pharmacological examples. Several factors modulate the biological response elicited by VP in different in vitro systems. Some of them, such as the adrenal steroids, increase the antidiuretic effects of VP (Handler et al., 1969; Schwartz and Kokko, 1980). Other agents, such as α_2-adrenergic agonists (Krothapalli et al., 1983), prostaglandins (Grantham and Orloff, 1968), bradykinin (Schuster et al., 1984), atrial natriuretic hormone, (Dillingham and Anderson, 1986), somatostatin (Forrest et al., 1980), and acetylcholine (Arruda and Sabatini, 1980), exert an inhibitory action. Among the mechanism whereby regulatory agents might modulate the cellular response to VP are the following (Morel et al., 1987): (*a*) an adenylate cyclase inhibition involving the so-called Ni (inhibiting N protein) subunit of the guanosine triphosphate-dependent coupling protein complex (pertussis toxin), (*b*) a decrease in the cAMP cell content resulting from phosphodiesterase activation, and (*c*) a modulation of the cell response due to an alteration in cytosol-free calcium concentration. It has been established for VP that the number of free receptors in target cell membranes coupled to the occupancy of these receptors may be reduced when the tissue has been previously exposed, either in vivo or in vitro, to a high concentration of the hormone before the measurements are made. This phenomenon, called down-regulation or desensitization, results from an increased rate of receptor internalization when the VP concentration has been greatly enhanced, i.e., when the fractional occupancy of the receptors is high. Rajerison et al. (1977) reported that the VP-sensitive adenylate cyclase activity in the membrane of the rat kidney medulla is greatly decreased after the injection or perfusion of pharmacological doses of AVP to the animals.

Examination of the ligand selectivity of the V_1 receptors in a number of tissues revealed striking similarities among these receptors. V_1 receptors were observed in aortic smooth muscle cells (Penit et al., 1983; Pearlmutter et al., 1985; Vittet et al., 1986a), mesangial cells (Jard et al., 1987b), adrenal glomerulosa cells (Guillon and Gallo-Payet, 1986), synaptosomal membrane from the hippocampus (Barberis, 1983; Audigier and Barberis, 1985), liver membranes (Cantau et al., 1980), reproductive organs (Meidan and Hsueh, 1985; Guillon et al., 1987; Maggi et al., 1988), platelets (Thomas et al., 1983; Pletscher et al., 1985; Thibonnier and Roberts, 1985; Vittet et al., 1986b; Launay et al., 1987), human peripheral spleen lymphocytes, and monocytes (Block et al., 1981; Wickramashinghe et al., 1982; Bell et al., 1988; Torres and Johnson, 1988; Elands, 1989). The same selectivity was found for ligand binding to VP receptors expressed in different areas of the central and peripheral nervous systems (Király et al., 1986; Tribollet at al., 1988b).

VP target cells usually contain large numbers of spare receptors (Jard, 1988). The well-established differences in sensitivity of various VP-sensitive cells to VP mostly reflect differences in the number of spare receptors rather than significant differences in the dissociation constant for VP binding (Jard, 1983a). It is also known that structural modification of the VP molecule can influence both its affinity and efficacy. In studies on the activity of the primary effectors of both VP receptors (phosphoinositide hydrolysis or adenylate cyclase) a progressive transition from full agonism to pure antagonism could be observed in a series of structurally related VP analogues (Butlen et al., 1978; Jard et al., 1986).

The distribution of the hormone-dependent adenylate cyclase activity exhibits marked species differences in certain nephron portions (Morel et al., 1981). Another problem occurs, depending on the mammalian species considered; structural modifications of the VP molecule can change its affinity for VP receptors to quite different extents. As a consequence, extrapolation of pharmacological data derived from studies at the receptor level to the in vivo situation, and vice versa, is hazardous.

New, and sometimes contradictory, data are published, depending on the methods applied for the determination of VP receptor capacity and on the various synthetic VP analogues used to demonstrate VP binding. This is demonstrated in the following discussion of the VP receptor characterization of the kidney, the brain and antidiuretic system, and the anterior pituitary.

Extensive pharmacological characterization of VP-binding sites has led to a clear distinction betwen the renal V_2 receptor type with cAMP as second messenger and the V_1 receptor with phosphatidyl-inositol as second messenger (Jard, 1983b). Elegant binding studies of [^{3}H] AVP binding in the rat kidney and its displacement by receptor subtype-specific VP analogues excluded the existence of V_1-specific receptor subtypes in the renal cortex (Tribollet et al., 1988a). There is, however, indirect evidence for the presence of both types of VP receptors in the rat medulla: VP stimulation of prostaglandin production in the medullary and epithelial cells is mediated by the V_1 receptor (Wuthrich and Vallotton, 1986).

Recently, Gertsberger and Fahrenholz (1989) studied the autoradiographic localization of V_1-binding sites in the rat kidney. Replacement of cysteine in position 1 of VP by Mca, and of the proline in position 7 by sarcosine, results in the formation of a potent V_1 antagonist,

(Mca[1],Sar[7])AVP, of both in vivo vasopressor activity (Gazis et al., 1984) and in vitro glycogenolytic activity (Fahrenholz et al., 1986). This analogue has high binding affinity for the hepatic V_1 receptor, but its affinity for the renal V_2 receptor is greatly decreased (Fahrenholz et al., 1984). The introduction of one labeled iodine on tyrosine in position 2 of the potent V_1 antagonist (Mca[1],Sar[7])AVP did not alter its binding affinity. When this method was used, V_1-specific binding sites could be demonstrated in the medullary compartment of the rat kidney (Gertsberger and Fahrenholz, 1989).

Another radioiodinated VP antagonist, Mca[1]Tyr-(Me)[2]NH_2[9]AVP, was prepared by Elands and his coworkers (1988) and exhibited a high antivasopressor activity. Iodination was carried out at the phenyl moiety of the tyrosylamid residue at position 9, followed by high-performance liquid chromatography purification and slightly reduced the antivasopressor potency. The VP antagonist and its iodinated counterpart inhibited [^{3}H]AVP binding to V_1 (liver) and V_2 (kidney medulla) VP receptors. Consistent with the previous in vivo data, high affinity for the V_1 receptor was found. The observation that the V_1 receptor-blocking $Mca_1Tyr(Me)^2Tyr-NH_2^9AVP$ also binds to renal V_2 receptors with high affinity was unexpected but also has been described by Van Leeuwen et al. (1987), who used a tritiated V_1 antagonist.

The presence of a V_1 receptor in the kidney was substantiated by another research group (Burnatowska-Hledin and Spielman, 1989). They found that the rapid and transient increases in cytosolic free calcium induced by AVP in the principal cells of the cortical collecting tubules could be blocked by a V_1-specific VP antagonist, whereas V_2-specific analogues did not reveal biological activity. The evidence for the presence of both V_1 and V_2 receptors in the renal medulla is documented by the authors cited earlier. Recently, Garg and Kapturczak (1990) published convincing arguments that V_1 receptors are not present in the inner medullary collecting duct cells but are probably present in the endothelial cells of the blood vessels and/or interstitial cells of the renal medulla. It was reported that OT produces diuresis and increases the fractional excretion of sodium in rats (Balment et al., 1982; Conrad et al., 1986). It has been suggested that OT produces these effects not only via haemodynamic changes in the kidney but also by its direct effect on the renal tubular cells. Stassen et al. (1988) identified and characterized specific OT-binding sites which probably represent the putative OT receptors of pig kidney cell line (LLC-PK_1). Garg et al. (1990) reported that VP stimulates phosphoinositide hydrolysis in LLC-PK_1 cells. However, OT and its agonist analogue also produced a significant increase in phosphoinositide hydrolysis in LLC-PK_1 cells through OT receptors that may be present in the kidney. It is possible that the renal tubular cells may respond to VP by their interaction with OT receptors rather than V_1 receptors.

The presence of a functional V_1 receptor system in neuronal tissue was suggested by extracellular electrophysiological recordings made in the lateral septum and hippocampus. Both in vitro (Albeck and Smock, 1988; Raggenbass et al., 1988) and in vivo (Joels and Urban, 1982) experiments revealed a significant increase in neuronal activity after VP administration. This action was minimized by the V_1 agonist (Phe[2],Orn[8])-vasotocin but not by a selection of V_2 agonists (Raggenbass et al., 1987). The iontophoretic application of AVP to structures around the proximal part of the third ventricle, a region important for central control of water metabolism, also induced neuronal firing rate, and only V_1 antagonists were able to block this response (Jeulin and Nicolaidis, 1988).

It was an interesting observation that V_1-specific binding sites could not be determined near the third ventricle, the VP-producing nuclei, and the neurohypophysis, as long as these structures were densely labeled with [^{3}H]AVP. On the basis of this study, the hypothesis was proposed that these hypothalamic areas have V_2-specific binding sites. This idea has recently been supported by Cheng and North (1989), who described reduced release of AVP from hypothalamic neurons in response to an increased plasma AVP level through an interaction with central V_2 receptors. It cannot be excluded that [^{3}H]AVP did not bind to a specific receptor entity in the magnocellular nuclei or the posterior pituitary (Yamamura et al., 1983; Junig et al., 1985; Gertsberger and Fahrenholz, 1989) but did to intrinsic neurophysins (Phillips et al., 1988). Different VP analogues with known binding potencies to neurophysin were applied in pharmacological studies by Dashwood and Robinson (1988) to displace [^{3}H]AVP from the rat posterior pituitary. The rank order of displacement could not be correlated with neurophysin binding. The presence of real binding sites for VP in the hypothalamoneurohypophyseal system and their pharmacological characteristics remain to be elucidated (Van Leeuwen and Wolters, 1983; Yamamura et al., 1983; Tribollet et al., 1988b).

Thus, it would appear that a large number of VP actions are mediated by the same subtype of VP receptor. An exception to this rule is the CRF-like effect of VP on ACTH release from the anterior pituitary. A large number of VP antagonists with a great variability in biological activity were used to study which relevant VP receptor is responsible for the CRF activity of VP. Several in vitro experiments have been directed at the characterization of the anterior pituitary VP receptor, because it cannot be ascertained from in vivo studies whether the ACTH- and β-endorphin-releasing activity of the analogues is due to a direct effect on the pituitary gland. These observations suggest that the structural requirements of the anterior pituitary VP receptor may be

different from both V_1 and V_2 receptors (Knepel et al., 1983, 1984a,b, 1986; Antoni, 1984; Antoni et al., 1984; Boertschli and Friedli, 1985).

The use of both V_1 and V_2 antagonists permitted the identification of a novel subtype of VP receptor in the anterior pituitary. Therefore, Jard et al. (1986) proposed that this receptor subtype should be named V_{1b} receptor, as opposed to an apparently common subtype of V_1 receptors (V_{1a} receptors) expressed in a number of VP-sensitive tissues. The anterior pituitary is the sole tissue in which V_{1b} receptors have been found.

The question arises of whether or not the natural hormones and their analogues have a specific affinity for different VP receptors. It is clear that VP receptors of the V_{1a}, V_{1b}, and V_2 subtypes discriminate quite efficiently between the two neurohypophyseal hormones. VP has a higher affinity for V_2 than for V_{1a} or V_{1b} receptors. Among the VP analogues with high antidiuretic activity, dDAVP remains one of the more selective ligands for V_2 receptors, but it discriminates very poorly among V_{1a}, V_{1b}, and OT receptors. Several potent antagonists of the VP response with low antidiuretic effect in vivo, such as $d(CH_2)_5AVP$ and $d(CH_2)_5Tyr(Me)AVP$, do discriminate efficiently between V_{1a} receptors and either V_2 or V_{1b} receptors. Most of the antagonists of the antidiuretic responses, however, discriminate very poorly between V_2 receptors and V_{1a} receptors but very efficiently between V_{1b} receptors and either V_2 or V_{1a} receptors (Jard, 1988).

Attempts to characterize VP receptor subtypes solely on the basis of their blockade by antagonists can give misleading data for several reasons (Manning et al., 1987a): (*a*) some analogues will block V_2 responses to VP in vitro but not in vivo; (*b*) none of the available antagonists is truly specific for V_1-, V_2-, or OT-like receptors (Manning and Sawyer, 1983; Sawyer and Manning, 1985). For example, although V_1 antagonists are highly specific for V_1 receptors and do not block V_2 receptors in vivo, they can, nonetheless, also block OT receptors. Also, all V_2 antagonists block V_1 and OT receptors with varying degrees of effectiveness; and (*c*) a few VP antagonists have been shown to exhibit species differences. Thus, dPTyr(Me)AVP, a V_1 antagonist in the rat (Bankowski et al., 1978), has been shown to be a weak antagonist in the dog (Liard et al., 1982). Also, $d(CH_2)_5Tyr(Et)VAVP$, a potent V_1 and V_2 antagonist in the rat (Manning et al., 1981b), exhibited only weak antidiuretic antagonism in the dog (Stassen et al., 1983). These data would, therefore, seem to indicate the value of antagonists in receptor discrimination studies and certainly point to the need for the design of selective agonists and antagonists for the novel VP receptor subtypes.

IV. Clinical Significance and Perspectives of Vasopressin Antagonist Treatment

VP antagonists have been used by hundreds of scientists worldwide to investigate the physiology and pathophysiology of VP in animals. More recently, these antagonists have also been used in human subjects.

Because it is now established that a specific VP antagonist may be effective in one species, and inactive in another (Kinter et al., 1987), one may question the nature of human VP receptors. Testing the vascular reactivity of VP and selective VP receptor antagonists at the level of isolated segments of human superior mesenteric arteries, Ohlstein and Berkowitz (1986) concluded that the VP receptors mediating vascular contraction in human mesenteric arteries were of the V_1 vascular type. Several lines of evidence have led to the conclusion that human platelet VP receptors are of the V_1 vascular type (Thibonnier, 1987a,b; Thibonnier et al., 1987). The above results indicate that human V_1 vascular VP receptors are similar to rat hepatic and mesenteric V_1 vascular VP receptors in terms of affinity and intracellular messenger (Thibonnier, 1988).

More limited observations of the V_2 renal VP receptors are available. However, competitive binding experiments performed with several VP analogues and measurement of VP-stimulated cAMP production by the human renal medulla (Kim and Schrier, 1985) indicate that human V_2 receptors are linked to adenylate cyclase in a fashion similar to that of rat medullary kidney V_2-type receptors (Stassen et al., 1982). Finally, it can be concluded that human VP receptors also can be classified into two groups, the V_1 vascular receptors linked to phosphatidylinositols and calcium mobilization and the V_2 renal receptors linked to adenylate cyclase (Thibonnier, 1988).

The following situations may be appropriate for the use of VP antagonists in human diseases: (*a*) The blockade of V_1 receptors is desirable in diseases characterized by VP-induced increases in total peripheral resistance and alteration of local blood flow. For instance, there is sufficient evidence that VP is involved in the increase in peripheral resistance in some cases of congestive heart failure (Bichet and Schrier, 1985; Goldsmith, 1987), in familial hypertension (Wyse, 1985), in bilateral renal cortical necrosis (Kocsis et al., 1987a,b), and, perhaps, in the development of gastric ulcer (László et al., 1990). (*b*) The blockade of V_2 receptors is indicated in diseases characterized by an excessive renal reabsorption of free water under the control of VP. V_2 antagonist administration may correct the fluid retention and hyponatriaemia observed during the hyperactivity of VP-secreting tumors in Schwartz-Bartter syndrome, congestive heart failure, liver cirrhosis, nephrotic syndromes, central nervous injuries, acute psychotic states, lung disease, etc. (*c*) Recent data demonstrate that VP stimulates platelet aggregation (Thibonnier and Roberts, 1985) and blood coagulation factor release (Kothler et al., 1986). These effects are beneficial in haemophiliac patients after tooth extraction (Mannucci et al., 1977) but may become detrimental in other situations, such as in postoperative patients with abnormal thromboembolic environments

(Grant et al., 1985) or in cigarette smokers with hyperaggregability of blood platelets and an enhanced blood coagulation profile provoked by VP release. In the future, appropriate antagonist treatment may help to correct these abnormalities. (*d*) Finally, it has been described (Melin et al., 1986) that VP and OT are involved in the aetiology of dysmenorrhoeic uterine hyperactivity and premature labour. Recently, there have been efforts to develop specific VP and OT antagonists that could be introduced for the treatment of dysmenorrhoea and premature labour.

In the present review points *a* and *b* will be evaluated, but there is insufficient information regarding points *c* and *d*. Among the V_1 antagonists, d(CH_2)$_5$Tyr(Me)AVP has been generally used for human experiments. In normal human subjects, this antagonist affected neither the BP nor the heart rate. Skin blood flow, as a sensitive indicator of the regional vasoconstrictor effects of AVP, also remained unchanged (Hofbauer et al., 1984b). Similar negative results were noted when 25 mg of the angiotensin-converting enzyme inhibitor captopril was given to the same subjects. It was concluded that unstimulated endogenous VP is not actively involved in the cardiovascular homeostasis of normally hydrated normotensive subjects in basal conditions and does not participate in the regulation of the BP, even if the renin-angiotensin system is blocked (Bussien et al., 1984). This V_1 antagonist blocked the pressor effects of exogenous VP in human subjects at the same doses as in rats and dogs (Bussien et al., 1984; Gavras et al., 1984). Waeber et al. (1986) have shown that a single 5-μg/kg bolus i.v. dose of V_1 antagonist is capable of blocking the vascular response to exogenous VP (1 munit/kg/min) for 2 h, therefore confirming the specificity and potency of this analogue in human subjects.

In contrast the V_2 agonist dDAVP caused a decrease in BP and an increase in heart rate in healthy volunteers (Derkx et al., 1983). Although many in vitro experiments have shown that dDAVP can block various V_1 receptor-mediated effects of VP, it is doubtful whether the effects observed in humans can be attributed to a V_1 receptor blockade. It is more likely that these effects are due to V_2 receptor stimulation, because both dDAVP and another V_2 agonist, dVDAVP, were shown to decrease the BP and increase the heart rate in dogs (Liard, 1990). Hirsch et al. (1989) showed that intraarterial AVP or dDAVP infusion increased the forearm blood flow in normal humans. These findings suggest that the forearm vasodilation may be mediated by V_2 vasopressinergic receptors. The existence of extrarenal V_2 receptors that possess the vasodilatory effect of VP was observed in several other studies (Schwartz et al., 1985b; Liard, 1986; Walker, 1986; Bichet et al., 1988).

During recent years, the effects of V_1 antagonists were studied in subjects with normal and elevated plasma AVP levels. A V_1 antagonist was administered (5-μg/kg i.v. bolus) to eight untreated patients with mild essential hypertension, normal plasma AVP levels, and normal cardiac and renal functions. There was no change in BP, heart rate, or skin blood flow after administration of the V_1 antagonist (Bussien et al., 1986b). It was, therefore, concluded that normal circulating AVP does not contribute to the increase of BP in patients with mild essential uncomplicated hypertension and normal plasma AVP levels. Other procedures, such as the volume loss induced by a Finnish sauna, proved to be insufficient to induce a marked and persistent increase of plasma AVP. Accordingly, the V_1 antagonist did not produce any haemodynamic effects (Bussien et al., 1986a).

A. Effects of V_1 Antagonists in Subjects with Elevated Plasma Arginine-Vasopressin Levels

A significant elevation of the plasma AVP level (from 1.3 ± 1 to 12.7 ± 3.4 pg/ml, mean ± SEM) was observed in 12 healthy cigarette smokers within 10 min after smoking two cigarettes (Waeber et al., 1984). The BP and heart rate were sometimes increased, and the skin blood flow was reduced. There was a significant relationship between the skin blood flow reduction and the elevation of AVP levels achieved after cigarette smoking. The prior administration of a V_1 antagonist (5 μg/kg i.v.) prevented the skin blood flow decrease induced by smoking. However, the increases in BP and heart rate remained unchanged. Waeber et al. (1984) concluded that the reduction in skin blood flow was due to an increased VP secretion induced by smoking and was specifically antagonized by the V_1 antagonist.

Seven patients with severe hypertension and end-stage renal disease, receiving an intravenous sodium load, were treated with a V_1 antagonists (0.5-mg i.v. bolus). The saline infusion markedly elevated the plasma AVP levels, whereas the V_1 antagonist induced a moderate reduction of BP (Gavras et al., 1984). In the next experimental series, the effects of blockade of the renin-angiotensin system (100 mg captopril), of the sympathetic nervous system (0.3–0.8 mg clonidine), and of VP (0.5 mg i.v. V_1 antagonist) were investigated in 14 patients with severe hypertension (Ribeiro et al., 1986). Each agent alone could induce a slight BP reduction (8–15 mm Hg). The hypotensive effect of the V_1 antagonist was not altered by captopril pretreatment, but it was potentiated by clonidine administration (12–15 mm Hg). The BP reduction induced by the V_1 antagonist was independent of the preexisting plasma AVP levels, but it was inversely correlated to the plasma norepinephrine levels. These observations point to a partial dependence of the BP on VP in patients with severe hypertension and to the role of VP in the maintenance of the vascular tone when the sympathetic nervous system activity is decreased.

In congestive heart failure, the V_1 antagonist induced a significant vasodilation only in those patients having increased plasma AVP levels (four of 20 patients). In patients with normal or slightly elevated AVP levels, the

BP and heart rate remained unchanged. When measurements from all the patients were considered, the reduction in systemic vascular resistance induced by the V_1 antagonist was correlated with the initial plasma AVP levels (Nicod et al., 1985; Creager et al., 1986).

On the basis of these observations, the blockade of V_1 receptors seems a beneficial therapeutic tool in patients with hypertension or congestive heart failure in the presence of increased plasma AVP levels. However, we do not have experience yet regarding the chronic use of V_1 antagonists in humans.

B. Therapeutic Effects of V_2 Antagonists

No suitable V_2 antagonist is available yet for clinical use. Many efforts have been made in Manning's laboratory to develop a synthetic highly potent specific V_2 antagonist (cf. section II.E). The VP antagonist $d(CH_2)_5$D-Tyr(Et)^{2}Val^{4}desGly^{9}AVP is the most potent in vitro antagonist of squirrel monkey and human VP-stimulated renal adenylate cyclase (Stassen et al., 1984). It also antagonized exogenous VP-stimulated antidiuresis in conscious water-loaded rats (Kinter et al., 1986). However, preliminary results indicated that this compound behaved in vivo in humans as a V_2 antagonist with partial V_1 antagonist and V_2 agonist activities (Thibonnier, 1988). Consequently, there are at present no data concerning the use of a specific and potent V_2 antagonist in human diseases.

From a theoretical point of view, SIADH would be an obvious indication for a V_2 antagonist (Schrier and Kim, 1984; Kinter et al., 1985; Thibonnier, 1988). Classic SIADH was described in two patients with bronchogenic carcinoma (Schwartz et al., 1957). The main clinical features of this syndrome are severe hyponatriaemia and renal sodium wasting. Zerbe et al. (1980) have reviewed the role of VP in 43 patients with SIADH. They identified four patterns of AVP (antidiuretic hormone) release: erratic secretion, reset osmostat, continuous VP leak, and antidiuresis with reduced VP values. Abnormal VP regulation could be established in the first three groups, but in the fourth group (14% of the patients) no abnormality in VP release could be identified.

It is notable, however, that the pathogenesis of SIADH is different in the various states of the disease. In the original description, the authors supposed that the malignant tumour tissue itself elaborated VP (Schwartz et al., 1957). Later, the VP activity of tumour tissue could not be determined in the majority of patients with SIADH and small cell carcinoma (Vorherr et al., 1968). Other mechanisms are probably responsible for the elevated AVP levels in tumour-associated SIADH (Zerbe et al., 1980). SIADH was also found in disorders of the central nervous system, pulmonary disease (as a result of drugs or surgery), psychosis, endocrine disease, and other conditions summarized in table 4 (Raskind et al., 1978; Skowsky and Kikuchi, 1978; Zerbe et al., 1980; Stassen et al., 1984).

Adequate therapy of SIADH has not yet been resolved. Several therapies have been reported in patients with the syndrome and include hypertonic saline (Hantman et al., 1973), Dilantin (Tanay et al., 1979), urea (Decaux et al., 1980), and furosemide (Decaux et al., 1982). If the patient is compliant and asymptomatic, fluid restriction is still the treatment of choice (Schrier, 1985).

Cherril et al. (1975), De Troyer (1977), and Forrest et al. (1978) reported that demeclocycline was superior to lithium in the treatment of chronic SIADH. However, Schrier (1978) indicated that, because demeclocycline causes nephrogenic diabetes insipidus and nephrotoxicity in patients with cardiac (Zegers de Beyl et al., 1978) or hepatic (Miller et al., 1980) disease, the utility of this drug as a treatment in hyponatriaemic states might be limited. The development of clinically effective V_2 antagonists would be an interesting therapeutic advance in the treatment of patients with SIADH. The selective increase of water excretion by V_2 aquaretic antagonists would make it possible to treat disorders of water homeostasis without affecting the electrolyte balance (Stassen et al., 1984; Schrier, 1985; Hofbauer and Mah, 1987; Thibonnier, 1988).

Recently, the term SIADH has been introduced to designate any clinical state in which hyponatriaemia is present. However, many cases of hyponatriaemia cannot be classified as SIADH because they are related to changes in ECF volume, which regulates VP secretion (Robertson et. al., 1973). From the aspect of the clinical approach to treating hyponatriaemia, it is important to determine the status of the ECF (Narins et al., 1982).

Patients with hyponatriaemia and a decreased ECF volume may suffer from NaCl loss through the gastrointestinal tract, skin, or kidneys. These patients have hypotension and low urine sodium excretion and respond well to physiological saline infusions. In these cases, the aquaretic therapy would not be beneficial. In sodium-retaining disorders (congestive heart failure, liver disease, nephrotic syndrome), the patients have an expanded ECF volume. However, the effective blood volume is generally reduced in these diseases, which increases AVP secretion (Iaina et al., 1980; Bichet and Manzini, 1984). These patients are frequently treated with conventional diuretics that induce hyponatriaemia. Hyponatriaemic patients with an expanded ECF volume would benefit from V_2 antagonist therapy. Finally, hyponatriaemia may develop with a relatively normal ECF volume in psychotic patients or patients with renal failure and severe potassium depletion. Such patients would also be candidates for aquaretic therapy.

Elevated AVP levels have been reported in congestive heart failure (Yamane, 1968, Szatalowicz et al., 1981; Riegger et al., 1982; Rondeau et al., 1982). Hyponatriaemia is more common and more severe in older patients with chronic heart failure (Rondeau et al., 1982) or after diuretic therapy. Aquaretic compounds might be benefi-

TABLE 4
*Disorders associated with SIADH**

Malignant tumors	Drugs
Carcinoma of the lung	Vasopressin
Carcinoma of the duodenum	Cisplatin
Carcinoma of the pancreas	Vincristine, vinblastine
Thymoma	Chloropropamide
Mesothelioma	Thiazide diuretics
Carcinoma of the bladder	Phenothiazines
ffiarcinoma of the ureter	Monoamine oxidase inhibitors
Prostatic carcinoma	Carbamazepine
Ewing's sarcoma	Clofibrate
Disorders of the central nervous system	Nicotine
Meningitis	Imipramine
Head trauma	Tricyclic antidepressants
Brain abscess	Acute psychosis
Brain tumors	Postoperative period
Encephalitis	Endocrine diseases
Guillain-Barré syndrome	Hypothyroidism
Acute intermittent porphyria	Adrenocortical insufficiency
Subarachnoid hemorrhage	Congestive heart failure
Cerebellar and cerebral atrophy	Liver cirrhosis
Cavernous sinus thrombosis	Burn injury
Neonatal hypoxia	Nephrosis
Hydrocephalus	Lupus erythematosus
Shy-Drager syndrome	Preterm infants
Diseases of the lung	Idiopathy
Pneumonia	
Tuberculosis	
Cavitation	
Emphysema	
Cystic fibrosis	
Pneumothorax	
Asthma	
Positive pressure breathing	

* Modified from Zerbe et al. (1980) and used with permission from Annual Review of Medicine, vol. 31, 1980.

cial in patients with hyponatriaemic congestive heart failure and elevated plasma AVP levels. Increased AVP release also has been reported in cirrhotic patients in whom plasma albumin and urine flow rate were reduced (Bichet et al., 1982a,b). The increased AVP level, which supports circulatory stability, may result in excessive water retention, hypotonicity, brain swelling, and neurological impairment. V_2 antagonist treatment would be useful to remove excess body water in cirrhotic patients with an elevated AVP level. It is important, however, to prevent hypernatriaemia during the treatment.

VP is also involved in neuropsychiatric disorders (Dorsa and Raskind, 1985). Self-induced water intoxication is reported primarily in persons with psychotic disease (Barahal, 1938; Murphy and Zelman, 1964; Alexander et al., 1973; Raskind, 1974; Raskind et al., 1975; Smith and Clark, 1980). Although rather rare in nonpsychotic patients, this syndrome may be relatively frequent in chronic psychiatric persons. Jose and Perez-Cruet (1979) reported that eight of 239 psychiatric patients had an episode of self-induced water intoxication. Six of these patients were schizophrenic. Another study in a chronic psychiatric hospital revealed 20 patients with significant hyponatriaemia secondary to polydipsia (Hariprasad et al., 1980). Many of the patients with water intoxication were treated with maintenance antipsychotic therapy. It has, therefore, been hypothesized that antipsychotic drugs may be a nonosmolar stimulus to VP secretion (Matuk and Kalyanaraman, 1977). However, the withdrawal of antipsychotic drugs proved unsuccessful (Miller et al., 1973; Fischman, 1975; Fowler et al., 1977; Kendler et al., 1978; Kosten and Camp, 1980). In only two cases, rechallenge with the antipsychotic drugs has suggested an association between the medications and impaired free water clearance (Ajlouni et al., 1974; Peck and Shenkman, 1979). Several reports suggest that antipsychotic treatment can prevent the development of dilutional hyponatriaemia in psychotic patients (Dubovsky et al., 1973; Hariprasad et al., 1980). Raskind et al. (1975) reported a nontreated psychotic patient with SIADH, in whom an inappropriately high plasma AVP concentration was documented. A special form of SIADH (reset osmostat for suppression of VP) was described in seven schizophrenic patients with dilutional hyponatriaemia and psychogenic polydipsia (Hariprasad et al., 1980). The major consequences of severe hyponatriaemia are brain swelling associated with depression of the sensorium and seizures (Arieff et al., 1976).

Finally, it has been shown that an aquaretic VP antagonist could prevent the severe hyponatriaemia and brain oedema (SIADH) induced by pitressin in rats (László et al., 1984b). VP antagonists have been used for the rapid reversal of mild hyponatriaemia associated with SIADH in rats without observable neurogenic symptoms (Kinter et al., 1984a). After occlusion of both cerebral common arteries for 4 h, the water content of the forebrain was increased in rats; this brain oedema was completely prevented by the administration of a V_2 antagonist (Tang and Ho, 1988).

On the basis of the above arguments, it can be concluded that VP antagonists, directed at the renal epithelial VP receptors, will probably be therapeutically useful drugs for the treatment of SIADH, hyponatriaemia, congestive heart failure, cirrhosis, nephrotic syndrome, and brain oedema associated with excessive VP and/or excessive ECF (Kinter et al., 1985).

V. Conclusions

On the basis of pharmacological and clinical experience, we have long known a potent V_1 antagonist, $d(Ch_2)_5Tyr(Me)AVP$, that can block the vasopressor responses to AVP. In terms of future studies, we must face the challenge of designing and synthesizing a more potent and truly specific V_1 antagonist devoid of oxytocic antagonism and of antagonism for other VP receptors. The clinical introduction of V_2 antagonists seems rather problematic. There have been substantial improvements in the design of specific aquaretic antagonists, but it is evident that we have not succeeded yet in eliminating V_1 antagonism from the most specific V_2 antagonists. Peptide chemists have been engaged in extensive efforts to identify further simplifications and modifications with the aim of synthesizing more stable antagonistic molecules and thus, possibly, orally active. These are important considerations in the design of antagonists for extensive clinical introduction.

V_1 antagonists may reduce the systemic vascular resistance and increase the cardiac output without affecting the BP. The absence of a hypotensive response to a V_1 antagonist does not indicate that endogenous AVP does not exert vasoconstrictor effects. The vasoconstrictor effects of VP display regional differences, and this is reflected by a predominant effect of V_1 antagonists in VP-sensitive vascular beds, such as the blood vessels of the intestines and skin. The measurements of regional haemodynamic parameters might, therefore, reveal effects of V_1 antagonists, even if no changes in systemic haemodynamics are observed. However, the BP and the alterations in regional blood flow observed after the administration of a VP antagonist may be influenced by a counterregulatory (baroreflex) mechanism. The pressor response to exogenous VP can be reduced by the previous injection of V_1 antagonists.

After inhibition of angiotensin II production with converting-enzyme inhibitors or angiotensin II receptor antagonists, and after the administration of sympatholytic drugs, a significant and prolonged hypotensive response can be observed following V_1 antagonist treatment. A reduction in BP occurred in DOCA-salt hypertensive rats after the acute administration of a V_1 antagonist; this effect was more pronounced if the baroreceptor reflex response was prevented by sinoaortic deafferentation. A small, but significant, reduction in BP was observed when the V_1 antagonist was administered chronically to rats during the development of DOCA-salt hypertension. Our results permit the conclusion that V_1 antagonists can prevent VP-induced coronary vasoconstriction.

During pregnancy, the oestrogen level is elevated, and the sensitivity of the renal arteries to the vasoconstrictive effect of VP is increased. Severe bleeding may occur as a complication of child bearing in human beings, and this significantly elevates VP secretion. The marked renal vasospasm is responsible for the development of bilateral renal cortical necrosis. In an experimental model, the V_1 antagonist prevents the renal vasospasm and the consequent renal cortical necrosis after VP administration in rats pretreated with oestrogen. These observations permit the conclusion that treatment with a V_1 antagonist may be an important means of preventing human renal cortical necrosis.

Our observations appear to prove that endogenous VP plays an important role in the pathomechanism of ethanol-induced gastric haemorrhagic erosions. VP deficiency and V_1 antagonist exerted similar gastric protection during VP-induced vasospasm of the mucosal microcirculation. V_1 antagonists may offer new perspectives in the treatment of peptic ulcer disease.

V_2 antagonists are capable of blocking the antidiuretic effects of exogenous VP. The acute administration of a V_2 (aquaretic) antagonist to dehydrated or normally hydrated rats induces a marked transitory increase in urine excretion. VP has been implicated in the pathogenesis of experimental brain oedema, which can be prevented by the administration of a V_2 antagonist. These observations suggest a novel approach to the treatment of VP-induced cerebral oedema.

The participation of VP in the secretion of ACTH has been extensively studied. Some of these studies suggested that the ACTH-releasing potency of VP and its analogues correlated with its pressor activity, whereas other experiments failed to demonstrate such a correlation. In accordance with these data, the structural requirements of the anterior pituitary VP receptor may be different from those of both V_1 and V_2 receptors.

In studies of isolated human medullary and papillary collecting tubules, VP antagonists completely inhibited the stimulation of adenylate cyclase by VP, and the blockade of renal VP receptors in vitro correlated with the induction aquaresis in vivo. This mechanism does not apply to all VP-sensitive tissues. The experimental

data indicated that an increase in cytosolic free calcium plays an important role in the glycogenolytic and vasopressor responses to VP. Accordingly, two subtypes of VP receptors are distinguished. V_1 receptors have been observed in aortic smooth muscle cells, mesangial cells, adrenal glomerulosa cells, liver membranes, reproductive organs, platelets, human peripheral and spleen lymphocytes, monocytes, and particular areas in the central and peripheral nervous systems. V_2 receptors have been established in the kidney. Many contradictory data have been published, depending on the methods and various synthetic VP analogues used for the demonstration of VP binding.

Clinical observations suggest that the blockade of the V_1 vascular receptors is a beneficial therapeutic tool in patients with hypertension or congestive heart failure in the presence of elevated plasma VP levels. From a theoretical aspect, V_1 antagonist treatment may be a new method to prevent coronary vasoconstriction and the development of bilateral renal cortical necrosis and gastric ulcer.

Unfortunately, no suitable V_2 antagonist is available yet for clinical use. After careful consideration of the pathogenesis of different diseases involving impaired water metabolism, V_2 antagonists will probably be therapeutically useful drugs for the treatment of SIADH, hyponatriaemia, congestive heart failure, cirrhosis, nephrotic syndrome, and brain oedema associated with excessive VP and/or excessive ECF.

REFERENCES

ABRAMOW, M., BEAUWANS, R., AND COGAN, E.: Cellular events in vasopressin action. Kidney Int. **32** (suppl. 21): S56–S66, 1987.

AISENBREY, G. A., HANDELMAN, W. A., ARNOLD, P., MANNING, M., AND SCHRIER, R. W: Vascular effects of arginine vasopressin during fluid deprivation in the rat. J. Clin. Invest. **67:** 961–968, 1981.

AIZAWA, T., YASUDA, N., GREER, M. A., AND SAWYER, W. H.: In vivo adrenocorticortopin-releasing activity of neurohypophyseal hormones and their analogs. Endocrinology **110:** 98–104, 1982.

AJLOUNI, K., KERN, M. W., AND TURES, J. F.: Thiothixene-induced hyponatremia. Arch. Intern. Med. **34:** 1103–1105, 1974.

ALBECK, D., AND SMOCK, T.: A mechanism for vasopressin action in the hippocampus. Brain Res. **463:** 394–397, 1988.

ALBERT, W. C., AND HANDLER, J. S.: Effect of PGE_1, indomethacin, and polyphloretin phosphate on the toad bladder response to ADH. Am. J. Physiol. **226:** 1382–1386, 1974.

ALEXANDER, E. R., CROW, T. J., AND HAMILTON, S. M.: Water intoxication in relation to acute psychotic disorder. Br. Med. J. **1:** 89, 1973.

ALI, F. E., BRYAN, W., CHANG, H-L., HUFFMAN, W. F., MOORE, M. L., HECKMAN, G., KINTER, L. B., MCDONALD, J., SCHMIDT, D., SHUE, D., AND STASSEN, F. L.: Potent vasopressin antagonists lacking the proline residue at position 7. J. Med. Chem. **29:** 984–988, 1986.

ALI, F. E., CHANG, H-L., HUFFMAN, W. F., HECKMAN, G., KINTER, L. B., WEIDLEY, E. F., EDWARDS, R., SCHMIDT, D., SHUE, D. A., AND STASSEN, F. L.: Potent vasopressin antagonists modified at the carboxy-terminal tripeptide tail. J. Med. Chem. **30:** 2291–2294, 1987.

AL-OMAR AZZAWI, S., AND SHIRLEY, D. G.: Renal blood flow and its distribution following haemorrhage in the rat: the role of vasopressin. J. Physiol. (Lond.) **346:** 171–179, 1984.

ALTURA, B. M.: Significance of amino acid residues in vasopressin on contraction of vascular muscle. Am. J. Physiol. **219:** 222–229, 1970.

ALTURA, B. M.: Selective microvascular constrictor actions of some neurohypophyseal peptides. Eur. J. Pharmacol. **24:** 49–60, 1973.

ALTURA, B. M.: Dose-response relationship for arginine vasopressin and synthetic analogs on three types of rat blood vessels: possible evidence for regional differences in vasopressin receptor sites within a mammal. J. Pharmacol. Exp. Ther. **193:** 413–423, 1975.

ALTURA, B. M.: DPAVP: a vasopressin analog with selective microvascular and RES actions for the treatment of circulatory shock in rats. Eur. J. Pharmacol. **37:** 155–167, 1976a.

ALTURA, B. M.: Microcirculatory approach to the treatment of circulatory shock with a new analog of vasopressin (2-phenylalanine, 8-ornithine) vasopressin. J. Pharmacol. Exp. Ther. **198:** 187–196, 1976b.

ALTURA, B. M.: Evidence that endogenous vasopressin plays a role in circulatory shock: role for reticuloendothelial system using Brattleboro rats. Experientia **36:** 1080–1081, 1980.

ALTURA, B. M., AND ALTURA, B. T.: Actions of vasopressin, oxytocine and synthetic analogs on vascular smooth muscle. Fed. Proc. **43:** 80–86, 1984.

ALTURA, B. M., AND HERSHEY, S. G.: Effects of vasoactive drug therapy on microvascular injury in shock. Pharmacologist **7:** 144, 1965.

ALTURA, B. M., AND HERSHEY, S. G.: A structure-activity basis for vasotropic peptide therapy in shock. Adv. Exp. Med. Biol. **21:** 399, 1972.

ALTURA, B. M., HERSHEY, S. G., AND ALTURA, B. T: Microcirculatory actions of polypeptides and their use in the treatment of experimental shock. Adv. Exp. Med. Biol. **8:** 239, 1970.

ALTURA, B. M., HERSHEY, S. G., AND MAZZIA, V. D. B.: Microcirculatory approach to vasopressor therapy in intestinal ischemic (SMA) shock. Am. J. Surg. **111:** 186–192, 1966.

ALTURA, B. M., HERSHEY, S. G., AND ZWEIFACH, B. W.: Effect of a synthetic analogue vasopressin on vascular smooth muscle. Proc. Soc. Exp. Biol. Med. **119:** 258–261, 1965a.

ALTURA, B. M., HSU, R., MAZZIA, V. D. B., AND HERSHEY, S. G.: Influence of vasopressors on survival after traumatic, intestinal ischemia and endotoxin shock. Proc. Soc. Exp. Biol. Med. **119:** 389–393, 1965b.

ANDERSON, R. J., CHUNG, H. M., KLUGE, R., AND SCHRIER, R. W.: Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann. Intern. Med. **102:** 164–168, 1985.

ANDERSON, W. A., JR., AND BROWN, E.: The influence of arginine-vasopressin upon the production of adenosine-3′,5′-monophosphate by adenyl cyclase from the kidney. Biochim. Biophys. Acta **67:** 674–676, 1963.

ANDERSSON, K.-E., ARNER, B., HEDNER, P., AND MULDER, J. L.: Effects of 8-lysine-vasopressin and synthetic analogues on release of ACTH. Acta Endocrinol. **69:** 640–648, 1972.

ANDREWS, C. E., AND BRENNER, B. M.: Relative contributions of arginine vasopressin and angiotensin II to maintenance of systemic arterial pressure in the anesthetized water-deprived rat. Circ. Res. **48:** 254–258, 1981.

ANTONI, F. A.: Novel ligand specificity of pituitary vasopressin receptors in the rat. Neuroendocrinology **39:** 186–188, 1984.

ANTONI, F. A., HOLMES, M. C., MAKARA, G. B., KÁRTESZI, M., AND LÁSZLÓ, F. A.: Evidence that the effects of arginine-8-vasopressin (AVP) on pituitary corticotropin (ACTH) release are mediated by a novel type of receptors. Peptides **5:** 519–522, 1984.

ARIEFF, A. I., LLACH, F., AND MASSRY, S. G.: Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine (Baltimore) **55:** 121–129, 1976.

ARIMURA, A., SAITO, T., BOWER, C. Y., AND SCHALLY, A. V.: Pituitary-adrenal activation in rats with hereditary hypothalamic diabetes insipidus. Acta Endocrinol. **54:** 155–165, 1967.

ARIMURA, A., SCHALLY, A. V., AND BOWER, C. Y.: Corticotropin releasing activity of lysine vasopressin analogues. Endocrinology **84:** 579–583, 1969.

ARNAULD, E., CZERNICHOW, P., FUMOUX, F., AND VINCENT, J.-D.: The effects of hypotension and hypovolaemia on the liberation of vasopressin during haemorrhage in the unanaesthetized monkey. Pflugers Arch. **371:** 193–200, 1977.

ARRUDA, J. A., AND SABATINI, S.: Cholinergic modulation of water transport in the toad bladder. Am. J. Physiol. **239:** F154–F159, 1980.

AUDIGIER, S., AND BARBERIS, C,: Pharmacological characterization of two specific binding sites for neurohypophyseal hormones in hippocampal synaptic plasma membranes of the rat. EMBO J. **4:** 1407–1412, 1985.

AYUS, J. C., KROTHOPALLI, R. K., AND ARIEFF, A. I.: Changing concepts in treatment of severe symptomatic hyponatremia: rapid correction and possible relation to central pontine myelinolysis. Am. J. Med. **78:** 897–902, 1965a.

AYUS, J. C., KROTHOPALLI, R. K., AND ARMSTRONG, D. L.: Rapid correction of severe hyponatremia in the rat: histopathological changes in the brain. Am. J. Physiol. **248:** F711–F719, 1985b.

BAERTSCHI, A. J., AND FRIEDLI, M.: A novel type of vasopressin receptor on anterior pituitary corticotrophs? Endocrinology **116:** 499–502, 1985.

BAERTSCHI, A. J., GAEHWILER, B. H., ANTONI, F. A., HOLMES, M. C., AND MAKARA, G. B.: No role of vasopressin in stress-induced ACTH secretion? Nature (Lond.) **308:** 85–86, 1984.

BAILLY, C., IMBERT-TEBOUL, M., CHABARDÈS, D., HUS-CITHAREL, A., MONTÉGUT, M., CLIQUE, A., AND MOREL, F.: The distal nephron of rat kidney: a target site for glucagon. Proc. Natl. Acad. Sci. USA **77:** 3422–3424, 1980.

BALMENT, R. J., BRIMBLE, M. J., AND FORSLING, M. L.: Oxytocin release and renal action in normal and Brattleboro rats. Ann. NY Acad. Sci. **394:** 241–253, 1982.

BANKOWSKI, K., MANNING, M., HALDAR., J., AND SAWYER, W. H.: Design of potent antagonists of the vasopressor response to arginine vasopressin. J. Med. Chem. **21:** 850–853, 1978.

BARAHAL, H. S.: Water intoxication in a mental case. Psychiat. Q. **12:** 767–771, 1938.

BARBERIS, C.: ^{3}H-Vasopressin binding to rat hippocampal synaptic plasma membrane: kinetic and pharmacologic characterization. FEBS Lett. **162:** 400–405, 1983.

BARTELSTONE, H. J., AND NASMYTH, P. A.: Vasopressin potentiation of catecholamine actions in dog, rat, cat, and rat aortic strip. Am. J. Physiol. **208:** 754–762, 1965.

BASTIDE, F., AND JARD, S.: Action of noradrenalin and oxytocin on the active

transport of sodium and the permeability on frog skin to water: role of cyclic AMP. Biochim. Biophys. Acta **150:** 113–123, 1968.

BAYLIS, P. H., AND HEATH, D. A.: Influence of presyncope and postural change upon plasma arginine vasopressin concentration in hydrated and dehydrated man. Clin. Endocrinol. **7:** 79–83, 1977.

BELL, J., GREENSTEIN, J. I., ADLER, M. W., AND LIU-CHEN, L-Y.: Binding characteristics of arginine vasopressin (AVP) on human peripheral blood mononuclear cells (PBMC) (abstr.). FASEB J. **2:** 1680, 1988.

BENNETT, T., AND GARDINER, S. M.: Involvement of vasopressin in cardiovascular regulation. Cardiovasc. Res. **19:** 57–68, 1985.

BENY, J.-L., AND BAERTSCHI, A. J.: Synthetic corticoliberin needs arginine vasopressin for full corticotropin releasing activity. Experientia **38:** 1078–1079, 1982.

BERDE, B., AND BOISSONNAS, R. A.: Basic pharmacological properties of synthetic analogues and homologues of the neurohypophyseal hormones. *In* Handbook of Experimental Pharmacology. Neurohypophyseal Hormones and Similar Polypeptides, ed. by B. Berde, pp. 802–870, Springer Verlag, Heidelberg, Germany, 1968.

BERDE, B., BOISSONNAS, R. A., HUGUENIN, R. L., AND STÜRMER, E.: Vasopressin analogues with selective pressor activity. Experientia **20:** 42–43, 1964.

BERECEK, K. H., BARRON, K. W., WEBB, R. L., AND BRODY, M. J.: Vasopressin-central nervous system interactions in the development of DOCA hypertension. Hypertension **4** (suppl. II): 131–137, 1982a.

BERECEK, K. H., MAH, S. C., BAUM, P., AND HOFBAUER, K. G.: Cardiovascular effects of intra-cerebroventricular injection of vasopressin in unanaesthetized normotensive and DOCA-salt hypertensive rats. J. Hypertens. **2:** 29–31, 1984a.

BERECEK, K. H., MURRAY, R. D., GROSS, F., AND BRODY, M. J.: Vasopressin and vascular reactivity in the development of DOCA hypertension in rats with hereditary diabetes insipidus. Hypertension **4:** 3–12, 1982b.

BERECEK, K. H., OLPE, H. R., JONES, R. S. G., AND HOFBAUER, K. G.: Microinjection of vasopressin into the locus coeruleus of conscious rats. Am. J. Physiol. **247:** H675–H681, 1984b.

BICHET, D., AND MANZINI, C.: Role of vasopressin (AVP) in the abnormal water excretion in nephrotic patients (NP). Kidney Int. **25:** 160, 1984.

BICHET, D., PUTTEN, V., AND SCHRIER, R. W.: Potential role of increased sympathetic activity impaired sodium and water retention in cirrhosis. N. Engl. J. Med. **307:** 1552–1557, 1982a.

BICHET, D., RAZI, M., LONERGAN, M., ARTHUS, M. F., PAPUKNA, V., KORTAS, C., AND BARJON, J. N.: Haemodynamic and coagulation responses to 1-deamino (8-D-arginine) vasopressin in patients with congenital nephrogenic diabetes insipidus. N. Engl. J. Med. **318:** 881–887, 1988.

BICHET, D., AND SCHRIER, R. W.: Role of vasopressin in abnormal water excretion in edematous disorders. *In* Vasopressin, ed. by R. W. Schrier, pp. 525–534, Raven Press, New York, 1985.

BICHET, D., SZTALOWICZ, V., CHAIMOVITZ, C., AND SCHRIER, R. W.: Role of vasopressin in abnormal water excretion in cirrhotic patients. Ann. Intern. Med. **96:** 413–417, 1982b.

BIE, P., AND WARBERG, J.: Effects of intravascular pressures of vasopressin and angiotensin. II. In dogs. Am. J. Physiol. **245:** R906–R914, 1983.

BLACKMORE, P. F., BRUMLEY, F. T., MARKS, J. L., AND EXTON, J. H.: Studies on alfa-adrenergic activation of hepatic glucose output: relationship between alfa-adrenergic stimulation of calcium efflux and activation of phosphorylase in isolated rat liver parenchymal cells. J. Biol. Chem. **253:** 4851–4858, 1978.

BLOCK, L. H., LOCHER, R., TENSCHERT, W., SIEGENTHALER, W., HOFFMANN, T., METTLER, R., AND VETTER, W.: ^{125}I-8-Z-arginine vasopressin binding to human mononuclear phagocytes. J. Clin. Invest. **68:** 374–381, 1981.

BOCKAERT, J., ROY, C., RAJERISON, L., AND JARD, S.: Specific binding of [^{3}H] lysine-vasopressin to pig kidney plasma membranes: relationship of receptor occupancy to adenylate cyclase activation. J. Biol. Chem. **248:** 5922–5931, 1973.

BRAND, P. H., METTING, P. J., AND BRITTON, S. L.: Support of arterial blood pressure by major pressure systems in conscious dogs. Am. J. Physiol. **255:** H483–H491, 1988.

BROWN, E., CLARKE, D. W., ROUX, V., AND SHERMAN, G. U.: The stimulation of adenosine-3′,5′-monophosphate production by antidiuretic factors. J. Biol. Chem. **238:** PC852–PC853, 1963.

BRUNNER, D. B., BURNIER, M., AND BRUNNER, H. R.: Plasma vasopressin in rats: effect of sodium, angiotensin, and catecholamines. Am. J. Physiol. **244:** H259–H265, 1983.

BURNATOWSKA-HLEDIN, M. A., AND SPIELMAN, W. S.: Vasopressin V_1 receptors on the principal cells of the rabbit collecting tubule. J. Clin. Invest. **83:** 84–89, 1989.

BURN, J. H.: Estimation of the antidiuretic potency of pituitary (posterior lobe) extract. Q. J. Pharm. **4:** 517–529, 1931.

BURNIER, M., BIOLLAZ, J. B., BRUNNER, D. B., AND BRUNNER, H. R.: Blood pressure maintenance in awake dehydrated rats: renin, vasopressin and sympathetic activity. Am. J. Physiol. **245:** H203–H204, 1983.

BURNIER, M., BIOLLAZ, J., BRUNNER, H. R., AND GAVRAS, H.: Vasopressin, blood pressure dependency after α-adrenoceptor blockade in normotensive and mineralocorticoid-salt hypertensive rats. Clin. Sci. **63** (suppl.): 101S–103S, 1982.

BURNIER, M., AND BRUNNER, H. R.: Pressor responses of rats to vasopressin: effect of sodium, angiotensin and catecholamines. Am. J. Physiol. **244:** H253–H258, 1983.

BUSSIEN, J. P., GAILLARD, R. C., NUSSBERGER, J., WAEBER, B., HOFBAUER, K. G., TURNILL, D., BROGGER, R., AND BRUNNER, H. R.: Haemodynamic role of vasopressin released during Finnish sauna. Acta Endocrinol. **112:** 166–171, 1986a.

BUSSIEN, J. P., WAEBER, B., NUSSBERGER, J., HOFBAUER, K. G., AND BRUNNER, H. R.: Blockade of the vascular effect of vasopressin in patients with mild essential hypertension. Arch. Int. Pharmacodyn. Ther. **282:** 130–139, 1986b.

BUSSIEN, J. P., WAEBER, B., NUSSBERGER, J., SCHALLER, M. D., GAVRAS, H., HOFBAUER, K., AND BRUNNER, H. R.: Does vasopressin sustain blood pressure of normally hydrated healthy volunteers? Am. J. Physiol. **246:** H143–H147, 1984.

BUTLEN, D., GUILLON, G., RAJERISON, R. M., JARD, S., SAWYER, W. H., AND MANNING, M.: Structural requirements for activation of vasopressin-sensitive adenylate cyclase and hormone binding: effects of highly potent antidiuretic analogues and competitive inhibitors. Mol. Pharmacol. **14:** 1006–1017, 1978.

BYROM, F. B.: Morbid effects of vasopressin on the organs and vessels of rats. J. Pathol. Bacteriol. **45:** 1–16, 1937.

BYROM, F. B.: Effect of oestrogenic and other sex hormones on response of rat to vasopressin. Lancet **1:** 129–131, 1938.

BYROM, F. B., AND PRATT, O. E.: Oxytocin and renal cortical necrosis. Lancet **1:** 753–754, 1959.

CALLAHAN, J. F., ASHTON-SHUE, D., BRYAN, H. G., BRYAN, W. M., HECKMAN, G. D., KINTER, L. B., MCDONALD, J. E., MOORE, M. L., SCHMIDT, D. B., SILVESTRI, J. S., STASSEN, F. L., SULAT, L., YIM, C. F., AND HUFFMAN, W. F.: Structure-activity relationship of novel vasopressin antagonists contains C-terminal diaminoalkanes and (amino-alkyl) guanidines. J. Med. Chem. **32:** 391–386, 1989.

CANTAU, B., KEPPENS, S., DEWULF, H., AND JARD, S.: [^{3}H]vasopressin binding to isolated rat hepatocytes and liver membranes: regulation by GTP and relation to glycogen phosphorylase activation. J. Recept. Res. **1:** 137–168, 1980.

CARLSON, D. E., DORNHORST, A., SEIF., S. M., ROBINSON, A. G., AND GANN, D. S.: Vasopressin-dependent and -independent control of the release of adrenocorticotropin. Endocrinology **110:** 680–682, 1982.

CARLSON, D. E., AND GANN, D. S.: Effects of vasopressin antiserum on the response of adrenocorticotropin and cortison to hemorrhage. Endocrinology **114:** 317–324, 1984.

CHAROCOPOS, F., HATZINIKOLAOU, P., NORTH, W. G., AND GAVRAS, H.: Systemic and regional haemodynamic effects of endogenous vasopressin stimulation in rats. Am. J. Physiol. **243:** H560–H565, 1982.

CHENG, S. W. T., AND NORTH, W. G.: Vasopressin reduces release from vasopressin-neurons and oxytocin-neurons by acting on V_2-like receptors. Brain Res. **479:** 35–39, 1989.

CHERRIL, D. A., STOTE, R. M., BIRGE, J. R., AND SINGER, I.: Demeclocycline treatment in the syndrome of inappropriate antidiuretic hormone secretion. Ann. Intern. Med. **83:** 654–656, 1975.

CHIEN, S., AND USAMI, S.: Rate and mechanism of release of antidiuretic hormone after hemorrhage. Circ. Shock **1:** 71–80, 1974.

COMMARATO, M. A., AND LUM, B. K. B.: Cardiovascular interaction of amphetamine and ephedrine with norepinephrine and with vasopressin. Eur. J. Pharmacol. **7:** 125–134, 1969.

CONRAD, K. P., GELLAI, M., NORTH, W. G., AND VALTIN, N.: Influence of oxytocin on renal haemodynamics and electrolyte and water excretion. Am. J. Physiol. **251:** F290–F296, 1986.

COWLEY, A. W., JR.: Perspectives on the physiology of hypertension. *In* Hypertension: Mechanisms, Diagnosis and Treatment, ed. by G. Onesti and A. N. Brest, pp. 1–22, F. A. Davis, Philadelphia, 1978.

COWLEY, A. W., JR.: Vasopressin and cardiovascular regulation. *In* Cardiovascular Physiology, vol. 4: International Review of Physiology, ed. by A. C. Guyton and J. E. Hall, pp. 189–242, University Park Press, Baltimore, 1982.

COWLEY, A. W., JR., AND BARBER, B. J.: Vasopressin vascular and reflex effects—a theoretical analysis. *In* The Neurohypophysis. Structure, Function and Control. Progress in Brain Research, vol. 60, ed. by B. A. Cross and G. Leng, pp. 415–424, Elsevier, Amsterdam, 1983.

COWLEY, A. W., JR., CUSHMAN, W. C., QUILLEN, E. W., JR., SKELTON, M. M., AND LANGFORD, H. G.: Vasopressin elevation in essential hypertension and increased responsiveness to sodium intake. Hypertension **3** (suppl. I): 93–100, 1981a.

COWLEY, A. W., JR., AND DE CLUE, J. W.: Quantification of baroreceptor influence on arterial pressure changes seen in primary angiotensin-induced hypertension in dogs. Circ. Res. **3:** 779–787, 1976.

COWLEY, A. W., JR., AND LIARD, J-F.: Cardiovascular actions of vasopressin. *In* Vasopressin, ed. by D. M. Gash and G. J. Boer, pp. 389–433, Plenum Press, New York, 1987.

COWLEY, A. W., JR., LIARD, J-F., SKELTON, M. M., QUILLEN, E. W., JR., AND WEBB, R. L.: Vasopressin-neural interactions in the control of cardiovascular function. *In* Vasopressin, ed. by R. W. Schrier, pp. 1–10, Raven Press, New York, 1985.

COWLEY, A. W., JR., MONOS, E., AND GUYTON, A. C.: Interaction of vasopressin and the baroreceptor reflex system in the regulation of the arterial pressure in the dog. Circ. Res. **34:** 505–514, 1974.

COWLEY, A. W., JR., SMITH, M. J., MANNING, R. D., AND LOHMEIER, T. E.: Pressor and volume effects of vasopressin. *In* Frontiers in Hypertension Research, ed. by J. H. Laragh, F. R. Buhler, and D. W. Seldin. p. 373, Springer Verlag, New York, 1981b.

COWLEY, A. W. JR., SWITZER, S. J., AND GUINN, M. M.: Evidence and quantification of the vasopressin arterial pressure control system in the dog. Circ. Res. **46:** 58–67, 1980.

COWLEY, A. W., JR., SWITZER, S. J., AND SKELTON, M. M.: Vasopressin, fluid, and electrolyte response to chronic angiotensin II infusion. Am. J. Physiol. **240:** R130–R138, 1981c.

CREAGER, M. A., FAXON, D. P., CUTLER, S. S., KOHLMANN, O., RYAN, T. J., AND GAVRAS, H.: Contribution of vasopressin to vasoconstriction in patients

with congestive heart failure: comparison with the renin-angiotensin system and the sympathetic nervous system. J. Am. Coll. Cardiol. **7:** 758–765, 1986.

CROFTON, J. T., SHARE, L., SHADE, R. E., LEE-KWON, W. J., MANNING, M., AND SAWYER, W. H.: The importance of vasopressin in the development and maintenance of DOC-salt hypertension in the rat. Hypertension, **1:** 31–38, 1979.

CROFTON, J. T., SHARE, L., WANG, B. C., AND SHADE, R. E.: Pressor responsiveness to vasopressin in the rat with DOC-salt hypertension. Hypertension **2:** 424–431, 1980.

CROSS, R. B., TRACE, J. W., AND VATTUONE, R. J.: The effect of vasopressin upon the vasculature of the isolated perfused rat kidney. J. Physiol. (Lond.) **239:** 435–442, 1974.

DASHWOOD, M. R., AND ROBINSON, I. C. A. F.: Specificity of vasopressin binding to the posterior gland in the rat. Neuroendocrinology **48:** 180–187, 1988.

DAVIES, R., FORSLING, M. L., AND SLATER, J. D. H.: The interrelationship between the release of renin and vasopressin as defined by orthostasis and propranolol. J. Clin. Invest. **60:** 1438–1441, 1977.

DAVIES, R., SLATER, J. D. H., FORSLING, M. L, AND PAYNE, N.: The response of arginine vasopressin and plasma renin to postural change in normal man, with observation on syncope. Clin. Sci. Mol. Med. **51:** 267–274, 1976.

DECAUX, G., BRIMIOULLE, S., GENETTE, F., AND MOCKEL, J.: Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. Am. J. Med. **69:** 99–106, 1980.

DECAUX, G., WATERLOT, Y., GENETTE, F., HULLEMOUS, R., AND DEMANET, J. C.: Inappropriate secretion of antidiuretic hormone treated with furosemide. Br. Med. J. **285:** 89–90, 1982.

DEKANSKI, J.: The quantitative assay of vasopressin. Br. J. Pharmacol. **7:** 567–572, 1952.

DERKX, F. H., MAN IN'T VELD, A. J., JONES, R., REID, J. L., AND SCHALEKAMP, M. A. D. H.: DDAVP (1-desamino-8-D-arginine vasopressin): an antagonist of the pressor action of endogenous vasopressin? J. Hypertens. **1** (suppl. 2): 58–61, 1983.

DE TROYER, A.: Demeclocycline: treatment for syndrome of inappropriate antidiuretic hormone secretion. JAMA **237:** 2723–2726, 1977.

DE WIED, D.: A simple automatic and sensitive method for the assay of antidiuretic hormone with notes on the antidiuretic potency of plasma under different experimental conditions. Acta Physiol. Pharmacol. Neerl. **9:** 69–81, 1960.

DE WIED, D.: The significance of the antidiuretic hormone in release mechanism of corticotrophin. Endocrinology **68:** 956–970, 1961.

DE WIED, D., SIDERIUS, P., AND MIRSKY, I. A.: The antidiuretic- and ACTH releasing effect of various octapeptides. Arch. Int. Pharmacodyn. **133:** 50–57, 1951.

DILLINGHAM, M. A., AND ANDERSON, R. J.: Inhibition of vasopressin action by atrial natriuretic factor. Science **231:** 1572–1573, 1986.

DOCZI, T. LÁSZLÓ, F. A., SZERDAHELYI, P., AND JOO, F.: Involvement of vasopressin in brain oedema formation: further evidence obtained from the Brattleboro diabetes insipidus rat with experimental subarachnoid hemorrhage. Neurosurgery **14:** 436–441, 1984.

DOCZI, T., JOO, F., LENGYEL, Z., AND LÁSZLÓ, F. A.: Prevention of brain oedema formation by administration of vasopressin antagonist in rats with experimental subarachnoid hemorrhage. Neurosurgery, in press, 1991.

DOEPFNER, W., STURMER, E., AND BERDE, B,: On the corticotrophin-releasing activity of synthetic neurohypophyseal hormones and some related peptides. Endocrinology **72:** 897–901, 1963.

DORSA, D. M., AND RASKIND, M. A.: Vasopressin in neuropsychiatric disorders. *In* Vasopressin, ed. by R. W. Schrier, pp. 535–542, Raven Press, New York, 1985.

DRAPANAS, T., CROW, C. P., SHIM, W. K. T., AND SCHENK, W. G.: The effect of pitressin on cardiac output and coronary, hepatic and intestinal blood flow. Surv. Gynecol. Obstet. **113:** 484–489, 1961.

DUBOVSKY, S. L., GRABON, S., BERL, T., AND SCHRIER, R. W.: Syndrome of inappropriate secretion of antidiuretic hormone with exacerbated psychosis. Ann. Intern. Med. **79:** 551–554, 1973.

DU VIGNEAUD, V., GASH, D. T., AND KATSOYANNIS, P. G.: A synthetic preparation possessing biological properties associated with arginine-vasopressin. J. Am. Chem. Soc. **76:** 4751–4752, 1954.

DYCKES, D. F., NESTOR, J. J., JR., FERGER, M. F., AND DU VIGNEAUD, V.: [1-β-Mercapto,β,β-diethyl propionic acid 8]-lysine-vasopressin a potent inhibitor of 8-lysine-vasopressin and of oxytocin. J. Med. Chem. **17:** 250–252, 1974.

DYTKO, G., AND KINTER, L. B.: Prevention of hyponatremia in experimental Schwartz-Bartter syndrome with the vasopressin antagonist Sk& 10 1926. Ann. NY Acad. Sci. **481:** 369–371, 1986.

EBERT, T. J., COWLEY, A. W., AND SKELTON, M.: Vasopressin reduces cardiac function and augments cardiopulmonary baroreflex resistance increases in man. J. Clin. Invest. **77:** 1136–1142, 1986.

EDWARDS, C. R. W.: Vasopressin. *In* Clinical Neuroendocrinology, ed. by L. Martini and G. M. Besser, pp. 527–567, Academic Press, New York, 1977.

ELANDS, J.: Neurohypophyseal Hormone Receptors. Ph. D. thesis, pp. 1–159, University of Utrecht, Utrecht, The Netherlands, 1989.

ELANDS, J., BARBERIS, C., JARD, S., LAMMEK, B., MANNING, M., SAWYER, W. H., AND KLOET, E. R.: [^{125}I]-d(CH_2)$_5$[Tyr(Me)^2, Tyr(NH_2)^9] AVP: iodination and binding characteristics of a vasopressin receptor ligand. FEBS Lett. **229:** 251–255, 1988.

ELIJOVICH, F., BARRY, C. R., KRAKOFF, L. R., AND KIRCHBERGER, M.: Differential effect of vasopressin on angiotensin and norepinephrine pressor action in rats. Am. J. Physiol. **247:** H973–H977, 1984.

ERICSSON, B. F.: Effect of vasopressin on the distribution of cardiac output and organ blood flow in the anaesthetized dog. Acta Chir. Scand. **137:** 729–738, 1971.

ERRINGTON, M. L., AND ROCHA E SILVA, M.: On the role of vasopressin and angiotensin in the development of irreversible haemorrhagic shock. J. Physiol. (Lond.) **242:** 119–141, 1974.

FAHRENHOLZ, F., BOER, R., CRAUSE, P., FRITZSCH, G., AND GRZONKA, Z.: Interactions of vasopressin agonists and antagonists with membrane receptors. Eur. J. Pharmacol. **100:** 47, 1984.

FAHRENHOLZ, F., KOJRO, E., MÜLLER, M., BOER, R., LÖHR, R., AND GRZONKA, Z.: Iodinated photoactive vasopressin antagonists: labeling of hepatic vasopressin receptor subunits. Eur. J. Biochem. **161:** 321–328, 1986.

FARINI, F.: Diabete insipido ed opoterapia. Gazz. Osped. Clin. **34:** 1135–1139, 1913.

FISCHMAN, C. M.: Water intoxication and thioridazine. Ann. Intern. Med. **82:** 852, 1975.

FLORES, A. G. A., AND SHARP, G. W.: Endogenous prostaglandins and osmotic water flow in the toad bladder. Am. J. Physiol. **223:** 1392–1397, 1972.

FORREST, J. N., JR., COX, M., HONG, C., MORRISON, G., BIA, M., AND SINGER, J.: Superiority of demeclocyclin over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. N. Engl. J. Med. **298:** 173–177, 1978.

FORREST, J. N., JR., REICHLIN, S., AND GOODMAN, D. B. P.: Somatostatin: an endogenous peptide in the toad urinary bladder inhibits vasopressin-stimulated water flow. Proc. Natl. Acad. Sci. USA **77:** 4984–4987, 1980.

FOWLER, R. C., KRONFOL, Z. A., AND PERRY, R. N.: Water intoxication, psychosis and inappropriate secretion of antidiuretic hormone. Arch. Gen. Psychiatry **34:** 1097–1099, 1977.

FRIEDEN, J., AND KELLER, A. D.: The release of vasopressin in response to haemorrhage and its role in the mechanism of blood pressure regulation. Circ. Res. **2:** 214–220, 1954.

FRIEDMAN, S. M., FRIEDMAN, C. L., AND NAKASHIMA, M.: Accelerated appearance of DOCA hypertension in rats treated with pitressin. Endocrinology **67:** 752–759, 1960.

GARDINER, S. M., AND BENNETT, T.: The control of heart in rats hereditary hypothalamic diabetes insipidus (Brattleboro strain). *In* The Brattleboro Rat, ed. H. W. Sorol and H. Valtin, Ann. NY Acad. Sci. 363–374, 1982.

GARDINER, S. M., AND BENNETT, T.: Brain neuropeptides: actions on central cardiovascular control mechanisms. Brain Res. Rev. **14:** 70–116, 1989.

GARG, L. C., AND KAPTURCZAK, E.: Stimulation of phosphoinositide hydrolysis in renal medulla by vasopressin. Endocrinology **127:** 1022–1027, 1990.

GARG, L. C., WOZNIAK, M., AND PHILLIPS, M. I.: Stimulation of phosphoinositide hydrolysis by oxytocin in renal epithelial cells. J. Pharmacol. Exp. Ther. **252:** 552–557, 1990.

GASH, D. M., AND BOER, G. J.: Vasopressin, Plenum Press, New York, 1987.

GAVRAS, H., HATZINIKOLAOU, P., NORTH, W. G., BRESNAHAN, M., AND GAVRAS, I.: Interaction of the sympathetic nervous system with vasopressin and renin in the maintenance of blood pressure. Hypertension **4:** 400–405, 1982.

GAVRAS, H., RIBEIRO, A. B., KOHLMAN, O., SARAGOCA, M., MULINARI, R. A., RAMOS, O., AND GAVRAS, I.: Effects of a specific inhibitor of the vascular action of vasopressin in humans. Hypertension **6** (suppl. I.): I156–I160, 1984.

GAZIS, D., SCHWARTZ, I. L., LAMMEK, B., AND GRZONKA, Z.: Influence of sarcosin or N-methylalanine in position 7 on the antagonistic properties of 1-deamino-penicillamine and 1-(mercapto,β-cyclopento-methylene-propionic acid) vasopressin. Int. J. Pept. Protein Res. **23:** 78, 1984.

GELLAI, M.: Vasopressin antagonists in studies on the role of vasopressin in renal haemodynamics. *In* Vasopressin, ed. by R. W. Schrier, pp. 167–170, Raven Press, New York, 1985.

GELLAI, M., BANKIR, L., AND GRÜNFELD, J. P. Vasopressin and renal haemodynamics: vascular and tubular effects. In Sixteenth Annual Meeting of the American Society of Nephrology, p. 150A, 1983.

GELLAI, M., SILVERSTEIN, J. H., HWANG, J. C., LA ROCHELLE, F. T., JR., AND VALTIN, H.: Influence of vasopressin on renal haemodynamics in conscious Brattleboro rats. Am. J. Physiol. **246:** F819–F827, 1984.

GELLAI, M., AND VALTIN, H.: Chronic vascular constriction and measurements of renal function in conscious rats. Kidney Int. **15:** 419–426, 1979.

GERKE, D. C., FREWIN, D. B., AND FROST, B. R.: The synergistic vasoconstrictor effect of octapressin and catecholamines on the isolated rabbit ear artery. Aust. J. Exp. Biol. Med. Sci. **55:** 737–740, 1977.

GERSTBERGER, R., AND FAHRENHOLZ, F.: Autoradiographic localization of V_1 vasopressin binding sites in rat brain and kidney. Eur. J. Pharmacol. **167:** 105–116, 1989.

GIGUERE, V., AND LABRIE, F.: Vasopressin potentiates cyclic AMP accumulation and ACTH release induced by corticotropin-releasing factor (CRF) in rat anterior pituitary cells in culture. Endocrinology **111:** 1752–1754, 1982.

GILLIES, G. E., LINTON, E. A., AND LOWRY, P. J.: Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. Nature (Lond.) **299:** 355–357, 1982.

GILLIES, G., AND LOWRY, P. J.: Corticotrophin releasing factor may be modulated vasopressin. Nature (Lond.) **278:** 463–464, 1979.

GILLIES, G., AND LOWRY, P. J.: Corticotrophin releasing activity in extracts of the stalk median eminence of Brattleboro rats. J. Endocrinol. (Lond.) **84:** 65–73, 1980.

GINSBURG, M., AND BROWN, L. M.: Effects of anesthetics and haemorrhage on the release of neurohypophysial antidiuretic. Br. J. Pharmacol. **11:** 236–244, 1956.

GOLDSMITH, S. R.: Vasopressin as vasopressor. Am. J. Med. **82:** 1213–1219, 1987.

GRANT, P. J., DAVIES, J. A., TATE, G. M., BOOTHBY, M., AND PRENTICE, C. R.

M.: Effects of physiological concentrations of vasopressin in haemostatic functions in man. Clin. Sci. **69:** 471–476, 1985.

GRANTHAM, J. J., AND BURG, M. B.: Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. Am. J. Physiol. **211:** 255–259, 1966.

GRANTHAM, J. J., AND ORLOFF, J.: Effect of prostaglandin E_1 on the permeability response of the isolated collecting tubule to vasopressin, adenosine-3′,5′-monophosphate and theophylline. J. Clin. Invest. **47:** 1154–1161, 1968.

GREGORY, L. C., QUILLEN E. W., JR., KEIL, L. C., CHANG, D., AND REID, T. A.: Effect of vasopressin blockade on blood pressure during water deprivation in intact and baroreceptor-denervated conscious dogs. Am. J. Physiol. **254:** E490–E495, 1988.

GROSS, P. A., PEHRISCH, H., RASCHER, P. W., HACKENTHAL, E., SCHÖMIG, A., AND RITZ, E.: Vasopressin in clinical hyponatremia: what stimuli? J. Cardiovasc. Pharmacol. **8** (suppl. 7): S92–S95, 1986.

GROSS, P. A., RASCHER, P. W., HACKENTHAL, E., AND RITZ, E.: Pathogenesis of clinical hyponatremia: observation of vasopressin and fluid intake 100 hyponatremic medical patients. Eur. J. Clin. Invest. **17:** 123–129, 1987.

GUILLEMIN, R.: A re-evaluation of acetylcholine, adrenaline, noradrenaline and histamine as possible mediators of the pituitary adrenocorticotrophic activation by stress. Endocrinology **56:** 248–255, 1955.

GUILLON, G., BALESTRE, M. N., ROBERTS, J. M., AND BOTTARI, S. P.: Oxytocin and vasopressin: distinct receptors in myometrium. J. Clin. Endocrinol. Metab. **64:** 1129–1135, 1987.

GUILLON, G., BUTLEN, D., BARTH, T., AND JARD, S.: Kinetic and pharmacological characterisation of vasopressin membrane receptors from human kidney medulla: relation to adenylate cyclase activation. Eur. J. Pharmacol. **85:** 291–304, 1982.

GUILLON, G., AND GALLO-PAYET, N.: Specific vasopressin binding to rat adrenal glomerulosa cells: relation to inositol lipid breakdown. Biochem. J. **235:** 209–214, 1986.

HANDLER, J. S., AND ORLOFF, J.: Antidiuretic hormone. Annu. Rev. Physiol. **43:** 611–624, 1981.

HANDLER, J. S., PRESTON, A. D., AND ORLOFF, J.: Effect of adrenal steroid hormones on the response of toads urinary bladder to vasopressin. J. Clin. Invest. **48:** 823–833, 1969.

HANTMAN, D., ROSSIER, B., ZOHLMAN, R., AND SCHRIER, R.: Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone: an alternative treatment to hypertonic saline. Ann. Intern. Med. **78:** 870–875, 1973.

HARIPRASAD, M. K., EISINGER, R. P., NADLER, I. M., PADMANABHAN, C. S., AND NIDUS, B. D.: Hyponatremia in psychogenic polydipsia. Arch. Intern. Med. **140:** 1639–1642, 1980.

HATZINIKOLAOU, P., GAVRAS, H., BRUNNER, H. R., AND GAVRAS, I.: Sodium-induced elevation of blood pressure in the anephric state. Science **209:** 935–936, 1980.

HATZINIKOLAOU, P., GAVRAS, H., BRUNNER, H. R., AND GAVRAS, I.: Role of vasopressin, catecholamines and plasma volume in hypertonic saline-induced hypertension. Am. J. Physiol. **240:** H827–H831, 1981.

HAYWOOD, J. R., SCHAFFER, R. A., FASTENOW, C., FINK, G. D., AND BRODY, M. J.: Regional blood flow measurement with pulsed Doppler flowmeter in conscious rat. Am. J. Physiol. **241:** H273–H278, 1981.

HECHTER, O., TERADA, S., SPITSBERG, V., NAKAHARA, T., NAKAGAWAGA, S. H., AND FLOURET, G.: Neurohypophyseal hormone-responsive renal adenylate cyclase. III. Relationship between affinity and intrinsic activity in neurohypophyseal hormones and structural analogs. J. Biol. Chem. **253:** 3230–3237, 1978.

HEMS, D. A., RODRIGUES, L. M., AND WHITTON, P. D.: Rapid stimulation by vasopressin, oxytocin and angiotensin II of glycogen degradation in hepatocyte suspensions. Biochem. J. **172:** 311–317, 1978.

HERSHEY, S. G., ALTURA, B. M., AND ORKIN, L. R.: Therapy of intestinal ischemic (SMA) shock with vasoactive drugs. Anesthesiology **29:** 466–470, 1968.

HERSHEY, S. G., MAZZIA, V. D. B., ALTURA, B. M., AND GYURE, L.: Effects of vasopressors on the microcirculation and on survival in hemorrhagic shock. Anesthesiology **26:** 179–189, 1965.

HERSHEY, S. G., MAZZIA, V. D. B., GYURE, L., AND SINGER, K.: Influence of a synthetic analogue of vasopressin on the survival after hemorrhagic shock in rats. Proc. Soc. Exp. Biol. Med. **115:** 325–328, 1964.

HEYNDRICKX, G. R., BOETTCHER, G. H., AND VATNER, S. F.: Effect of angiotensin, vasopressin and methoxamine on cardiac function and blood flow distribution in conscious dogs. Am. J. Physiol. **231:** 1579–1587, 1976.

HINOJOSA, C., AND HAYWOOD, J. R.: Contribution of vasopressin and the sympathetic nervous system in the early phase of high sodium-one kidney renal hypertension. Hypertension **6:** 848–854, 1984.

HIRSCH, A. T., DZAU, V. J., MAJZOUB, J. A., AND CREAGER, M. A.: Vasopressin mediated forearm vasodilatation in normal humans: evidence for a vascular vasopressin V_2 receptor. J. Clin. Invest. **84:** 418–426, 1989.

HIWATARI, M., NOLAN, P. L., AND JOHNSTON, C. I.: The contribution of vasopressin and angiotensin to the maintenance of blood pressure after autonomic blockade. Hypertension **7:** 547–553, 1985.

HOFBAUER, K. G., FORGIARINI, P., AND KERR, F.: Vasopressin receptor blockade and converting enzyme inhibition in glycerol-induced acute renal failure in rats. *In* Acute Renal Failure, ed. by D. Seybold, pp. 139–151, S. Karger, Basel, Switzerland, 1982.

HOFBAUER, K. G., AND MAH, S. C.: Vasopressin antagonists: present and future. Kidney Int. **32** (suppl. 21): S76–S82, 1987.

HOFBAUER, K. G., MAH, S. C., BAUM, H.-P., HANNI, H., WOOD, J. M., AND KRAITZ, J.: Endocrine control of salt and water excretion: the role of vasopressin in DOCA-salt hypertension. J. Cardiovasc. Pharmacol. **6** (suppl.): S184–S191, 1984a.

HOFBAUER, K. G., OPPERMAN, J. R., MAH, S. C., BAUM, H. P., WOOD, J. M., KRAETZ, J., AND KAMBER, B.: Chronic pharmacological blockade of vascular and tubular receptors of arginine vasopressin in rats. In Vasopressin, ed. by R. W. Schrier, pp. 159–165, Raven Press, New York, 1985.

HOFBAUER, K. G., STUDER, W., MAH, S. C., MICHEL, J. B., WOOD, J. M., AND STALDER, R.: The significance of vasopressin as a pressor agent. J. Cardiovasc. Pharmacol. **6:** S429–S438, 1984b.

HONORÉ, L. H.: Effects of single doses of deoxycorticosterone acetate (DOCA) and cortisone on vascular response of female rats to posterior pituitary hormones. Q. J. Exp. Physiol. **47:** 334–344, 1962a.

HONORÉ, L. H.: Vascular responses of male rats to post-pituitary hormones after treatment with deoxycorticosterone acetate (DOCA) and cortisone. Q. J. Exp. Physiol. **47:** 345–351, 1962b.

HOUCK, P. C., FIKSEN-OLSEN, M. J., BRITTON, S. J., AND ROMERO, J. C.: Role of angiotensin and vasopressin on blood pressure of ganglionic blocked dogs. Am. J. Physiol. **244:** H115–H120, 1983.

HOWELL, W. H.: The physiological effects of the hypophysis cerebri and infundibular body. J. Exp. Med. **3:** 245–258, 1898.

HUFFMAN, W. F., ALI, F. A., BRYAN, W. M., CALLAHAN, J. F., MOORE, M. L., SILVESTRI, J. S., YIM, N. C., KINTER, L. B., MCDONALD, J. E., ASHTON-SHUE, D., STASSEN, F. L., HECKMAN, G. D., SCHMIDT, D. B., AND SULAT, L.: Novel vasopressin analogues that help define a minimum effective antagonist pharmacophore. J. Med. Chem. **28:** 1759–1760, 1985.

HUGUENIN, R. L.: Synthese de la [Phe^2-Orn^8]-vasopressine et de la [Phe^2-Orn^8]-oxytocine, deux analogues de la vasopressine doués activité pressorique sélective. Helv. Chim. Acta **47:** 1934–1941, 1964.

HUGUENIN, R. L., AND BOISSONNAS, R. A.: Synthese de la [désamino^1-Arg^8]-vasopressine et de la [désamino^1-Phe^2-Arg^8]-vasopressine, deux analogues possedant une activité antidiurétique plus élevée et plus sélective que celle des vasopressines naturelles. Helv. Chim. Acta **49:** 695–705, 1966.

HUSAIN, M. K., FERNANDO, N., SHAPIRO, J., KIAGAN, A., AND GLICK, S. M.: Radioimmunassay of arginine vasopressin in human plasma. J. Clin. Endocriol. Metab. **37:** 616–625, 1973.

IAINA, A., ORNDORFF, M., GAVENDO, S., AND SOLOMON, S.: ADH effects in development of ischemic renal failure. Proc. Soc. Exp. Biol. Med. **163:** 206–211, 1980.

IMBERT, M., CHABARDÈS, D., MONTÉGUT, M., CLIQUE, A., AND MOREL, F.: Adenylate cyclase activity along the rabbit nephron as measured in single isolated segments. Pflugers Arch. **354:** 213–218, 1975.

IMBERT-TEBOUL, M., CHABARDÈS, D., CLIQUE, A., MONTÉGUT, M., AND MOREL, F.: Ontogenesis of hormone-dependent adenylate cyclase in isolated rat nephron segments. Am. J. Physiol. **247:** F316–F325, 1984.

ISHIKAWA, S. E., KIM, J. K., AND SCHRIER, R. W.: Further *in vivo* evidence for antagonist to antidiuretic action of arginine vasopressin. Am. J. Physiol. **245:** R713–R717, 1983.

ISHIKAWA, S. E., KIM, J. K., AND SCHRIER, R. W.: Effects of arginin vasopressin, antidiuretic and vasopressor antagonists in glucocorticoid and mineralocorticoid deficient rats. *In* Vasopressin, ed, by R. W. Schrier, pp. 171–180, Raven Press, New York, 1985.

ISHIKAWA, S. E., SAITO, T., OKADA, K., TSUTSUI, K., AND KUZUYA, T.: Effect of a vasopressin antagonist on water excretion in inferior vena cava constriction. Kidney Int. **30:** 49–55, 1986.

ISHIKAWA, S. E., AND SCHRIER, R. W.: Effect of arginin vasopressin antagonist on renal water retention in glucocorticoid and mineralocorticoid deficient rats. Kidney Int. **22:** 587–593, 1982.

ISHIKAWA, S. E., AND SCHRIER, R. W.: Vascular effects of arginine vasopressin, angiotensin II and norepinephrine in adrenal insufficiency. Am. J. Physiol. **246:** H104–H113, 1984.

JAFFERJI, S. S., AND MICHELL, R. H.: Stimulation of phosphatidyl-inositol turnover by histamine, 5-hydroxytriptamine and adrenaline in the longitudinal smooth muscle of guinea pig ileum. Biochem. Pharmacol. **25:** 1429–1430, 1976.

JAMISON, R. L., BUERKERT, J., AND LACY, F. B.: A micropuncture study of collecting tubule function in rats with hereditary diabetes insipidus. J. Clin. Invest. **50:** 2444–2452, 1971.

JAMISON, R. L., KIBERD, B., LARSON, T., ZIMMERHACKL, B., AND ROBERTSON, C. R.: The V_1 and V_2 receptor-mediated effects of arginine vasopressin on ascending and descending vasa recta blood flow. *In* Vasopressin: Cellular and Integrative Functions, ed. by A. W. Cowley, Jr., J-F. Liard, and D. A. Ausiello, pp. 143–148, Raven Press, New York, 1988.

JARD, S: Les isorcepteurs de la vasopressine dans le foie, dans le rein: relation entre fixation d'hormone et reponse biologique. J. Physiol. (Paris) **77:** 621–628, 1981.

JARD, S.: Vasopressin isoreceptors in mammals: relation to cyclic AMP-dependent and cyclic AMP-independent transduction mechanisms. In Current Topics in Membrane Transportation, vol. 18, ed. by A. Kleinzeller, pp. 255–285, Academic Press, New York, 1983a.

JARD, S.: Vasopressin: mechanisms of receptor activation. Progr. Brain Res. **60:** 384–394, 1983b.

JARD, S., GUILLON, G., BALESTRE, M. N., AND KIRK, C.: WRK1 cells: a model system for studying properties of V1a vasopressin receptors. J. Cardiovasc. Pharmacol. **8:**(suppl 7): S12–17, 1986.

JARD, S.: Mechanism of action of vasopressin and vasopressin antagonists. Kidney Int. **26** (suppl.): S38–S42, 1988.

JARD, S., GUILLON, G., GAILLARD, J. M. R., SCHOENENBERG, P., MULLER, A. F., MANNING, M., AND SAWYER, W. H.: Vasopressin antagonists facilitate the

discrimination of a novel vasopressin receptor sub-type in the rat adenohypophysis. Mol. Pharmcol. **30:** 171–177, 1986.

JARD, S., LOMBARD, C., MANNING, M., AND SAWYER, W. H.: Iodination of vasopressin analogues with agonistic and antagonistic properties: effects on biological properties and affinity for vascular and renal vasopressin receptors. Mol. Pharmacol. **32:** 367–375, 1987a.

JARD, S., LOMBARD, C., MARIE, J., AND DEVILLIERS, G.: Vasopressin receptors from cultured mesangial cells resemble V_{1a} type. Am. J. Physiol. **253:** F41–F49, 1987b.

JEULIN, A. C., AND NICOLAIDIS, S.: Evidence for vasopressin V_1 receptors of rostrodiencephalic neurons: iontophoretic studies in the *in vivo* rat: responses to oxytocin and angiotensin. Brain Res. Bull. **20:** 817–825, 1988.

JOELS, M., AND URBAN, I. J. A.: The effect of microiontophoretically applied vasopressin and oxytocin on single neurons in the septum and dorsal hippocampus. Neurosci. Lett. **33:** 79–84, 1982.

JOHNSTON, C. I., WOODS, R. L., NOLAN, P. L., AND IMAI, Y.: Vasopressin in blood pressure regulation. Excerpta Medica, Int. Congr. Ser. **398:** 349, 1983.

JONES, L. M., AND MICHELL, R. H.: Stimulus-response coupling at alpha-adrenergic receptors. Biochem. Soc. Trans. **6:** 673–688, 1978.

JONES, M. T., AND GILLHAM, B.: Factors involved in the regulation of adrenocorticotrophic hormone/, 3-lipotropic hormone. Physiol. Rev. **68:** 743–818, 1988.

JOSE, C. J., AND PEREZ-CRUET, J.: Incidence and morbidity of self-induced water intoxication in state mental hospital patients. Am. J. Psychiatry **136:** 221–222, 1979.

JUNIG, J. T., ABOOD, L. G., AND SKROBALA, A. M.: Two classes of arginine vasopressin binding sites on rat brain membranes. Neurochem. Res. **10:** 1187–1202, 1985.

KENDLER, K. S., WEITZMAN, R. E., AND RUBIN, R. T.: Lack of arginine vasopressin response to central dopamine blockade in normal adults. J. Clin. Endocrinol. Metab. **47:** 204–207, 1978.

KEPPENS, S., AND DE WULF, H.: The nature of the hepatic receptors involved in vasopressin-induced glycogenolysis. Bichim. Biophys. Acta **588:** 63–69, 1979a.

KEPPENS, S., AND DE WULF, H.: On the nature of the vasopressin receptors in the liver. Arch. Int. Physiol. Biochim. **87:** 189–190, 1979b.

KEPPENS, S., VANDENHEEDE, J. R., AND DE WULF, H.: On the role of calcium as second messenger in liver for the hormonally induced activation of glycogen phosphorylase. Biochim. Biophys. Acta **496:** 448–457, 1977.

KHOO, J. C., AND STEINBERG, D.: Stimulation of rat liver phosphorylase kinase by micromolar concentrations of Ca^{2+}. FEBS Lett. **57:** 68–72, 1975.

KIIL, F., AND AUKLAND, K.: The role of urea in the renal concentration mechanism. Scand. J. Clin. Lab. Invest. (Suppl.) **12:** 277–289, 1960.

KIM, J. K., AND SCHRIER, R. W.: Cellular effect of arginine vasopressin antagonist on the isolated renal tubule. *In* Vasopressin, ed. by R. W. Schrier, pp. 155–158, Raven Press, New York, 1985.

KINTER, L. B., CHURCHILL, S., STASSEN, F. L., MOORE, M., AND HUFFMAN, W.: Vasopressin antagonism in the squirrel monkey (*Saimiri sciurens*). J. Pharmacol. Exp. Ther. **241:** 797–803, 1987.

KINTER, L. B., DUBB, J., HUFFMAN, W., BRENNAN, F., AND STASSEN, F. L.: Potential role of vasopressin antagonists in the treatment of water-retaining disorders. *In* Vasopressin, ed. by R. W. Schrier, pp. 553–561, Raven Prees, New York, 1985.

KINTER, L. B., DYTKO, G., ASHTON, D., MCDONALD, J., HUFFMAN, W., AND STASSEN, F. L.: Discovery and therapeutical utility of vasopressin antagonists in rats. J. Cardiovasc. Pharmacol. **8** (suppl. 7): S36–S43, 1986.

KINTER, L. B., HUFFMAN, W. F., AND STASSEN, F. L.: Antagonists of antidiuretic activity of vasopressin. Am. J. Physiol. **254:** F165–F177, 1988.

KINTER, L. B., HUFFMAN, W. F., WIEBELHAUS, V. D., AND STASSEN, F. L.: Renal effects of aquaretic vasopressin analogs *in vivo*. *In* Diuretics, ed. by J. B. Puschett, pp. 72–81, Elsevier, Amsterdam, 1984a.

KINTER, L. B., MANN, W., HECKMAN, G., HUFFMAN, W. F., GROSS, M., AND STASSEN, F. L.: Vasopressin antagonist-associated aquaresis in dogs (abstr.). Kidney Int. **24:** 304, 1984b.

KIRÁLY, M., AUDIGIER, S., TRIBOLLET, E., BARBERIS, C., DOLIVO, M., AND DREIFUSS, J. J.: Biochemical and electrophysiological evidence of functional vasopressin receptors in the rat superior cervical ganglion. Proc. Natl. Acad. Sci. USA **83:** 5335–5339, 1986.

KIVILAAKSO, E., FROMM, D., AND SILEN, W.: Relationship between ulceration and intramural pH of gastric mucosa during hemorrhagic shock. Surgery **84:** 70–78, 1978.

KNEPEL, W., GÖTZ, D., AND FAHRENHOLZ, F.: Interaction of rat adenohypophyseal vasopressin receptors with vasopressin analogues substituted at position 7 and 1: dissimilarity from the V_1 vasopressin receptor. Neuroendocrinology **44:** 390–396, 1986.

KNEPEL, W., HOMOLKA, L., AND VLASKOVSKA, M.: In vitro CRF activity of vasopressin analogs is not related to pressor activity. Eur. J. Pharmacol. **91:** 115–118, 1983.

KNEPEL, W., HOMOLKA, L., VLASKOVSKA, M., AND NUTTO, D.: In vitro adrenocorticotropin/beta-endorphin-releasing activity of vasopressin analogs is related neither to pressor nor to antidiuretic activity. Endocrinology **114:** 1797–1804, 1984a.

KNEPEL, W., HOMOLKA, L., VLASKOVSKA, M., AND NUTTO, D.: Stimulation of adrenocorticotropin/beta-endorphin-release by synthetic ovine corticotropin releasing factor *in vitro*. Nueroendocrinology **38:** 344–350, 1984b.

KOCSIS, J., KARÁCSONY, G., KARCSU, S., AND LÁSZLÓ, F. A.: Histochemical and ultrastructural study of renal cortical necrosis in rats treated with oestrone + vasopressin, and its prevention with a vasopressin antagonist. Br. J. Exp. Pathol. **68:** 35–43, 1987a.

KOCSIS, J. SZABO, E., AND LÁSZLÓ, F. A.: Serio-angiographic study of renal cortical necrosis induced by administration of estrin + vasopressin in rats. Invest. Radiol. **14:** 295–299, 1979.

KOCSIS, J., SZABO, E., AND LÁSZLÓ, F. A.: Effect of a vasopressin antagonist $d(CH_2)_5Tyr(Me)$ AVP on the development of renal vasospasm induced by estrin plus vasopressin administration in rats. Invest. Radiol. **22:** 973–977, 1987b.

KOPIA, G. A., AND VOLOCIK, R. E.: Antagonism of vasopressin-induced coronary artery constriction by the vasopressin antagonist $d(CH_2)_5Tyr(Me)$ AVP. J. Cardiovasc. Pharmacol. **7:** 958–963, 1985.

KOSTEN, T. R., AND CAMP, W.: Inappropriate secretion of antidiuretic hormone in a patient receiving piperazine phenothiazines. Psychosomatics **21:** 351–355, 1980.

KOTHLER, M., HELLSTERN, P., MIYASHITA, C., VON BLOHN, G., AND WENZEL, E.: Comparative study of intranasae subcutaneous and intravenous administration of desamino-D-arginine vasopressin. Thromb. Haemost. **55:** 108–111, 1986.

KOVÁCS, K., DÁVID, M. A., AND LÁSZLÓ, F. A.: Effect of hypophysectomy on the development of renal cortical necrosis induced by posterior pituitary extract in oestrone pretreated rats. Br. J. Exp. Pathol. **45:** 415–418, 1964.

KOVÁCS, K., LÁSZLÓ, F. A., SÖVÉNYI, E., AND KOCSIS, J.: Angio-renographic studies in living rats during the development of renal cortical necrosis. Br. J. Radiol. **38:** 148–151, 1965.

KROTHAPALLI, R. K., DUFFY, W. B., SENEKJIAN, H. D., AND SUKI, W. N.: Modulation of the hydro-osmotic effect of vasopressin on the rabbit cortical collecting tubule by adrenergic agents. J. Clin. Invest. **72:** 287–294, 1983.

KRUSZYNSKI, M., LAMMEK, B., MANNING, M., SETO, J., HALDAR, J., AND SAWYER, W. H.: [1(beta-mercapto-beta-cyclopentamethylenepropionic acid)2-(O-methyl) tyrosine] arginine-vasopressin and [1-(beta-mercapto-beta, beta-cyclopentamethylenepropionic acid)] arginine-vasopressin, two highly potent anatgonists of the vasopressor response to arginine-vasopressin. J. Med. Chem. **23:** 364–368, 1980.

LACZI, F., JANÁKY, T., IVÁNYI, T., JULESZ, J., AND LÁSZLÓ, F. A.: Osmoregulation of arginine-8-vasopressin secretion in primary hypothyroidism and in Addison's disease. Acta Endocrinol. **114:** 389–395, 1987.

LADEFOGED, J., AND MUNCK, O.: Distribution of blood flow in the kidney. In Kidney Hormones, ed. by J. W. Fischer, Academic Press, New York, 1971.

LÁSZLÓ, F., KARÁCSONY, G., BALÁSPIRI, L., AND LÁSZLÓ, F. A.: The role of vasopressin in the pathomechanism of ethanol-induced gastric hemorrhagic erosions in rats. Gastroenterology, in press, 1991.

LÁSZLÓ, F., KARÁCSONY, G., NÁFRÁDI, J., RENGEI, B., VECSERNYÉS, M., LACZI, F., SZARVAS, F., LENGYEL, Z., AND LÁSZLÓ, F. A.: A high dose of ethanol releases vasopressin and simultaneously induces lesions in the rat stomach—the role of vasopressin in gastric cytoprotection. In New Aspects of Morphology, Function and Regulation. Proceedings of the 4th Conference on Neurohypophysis, Copenhagen, 1989, pp. 159–161, Oxford University Press, Oxford, England, 1989.

LÁSZLÓ, F. A.: Renal Cortical Necrosis. Experimental Induction by Hormones, S. Karger, Basel, Switzerland, 1981.

LÁSZLÓ, F. A., AND BALÁSPIRI, L.: Experimental water intoxication induced by dDAVP in rat, and its prevention with the vasopressin antagonist $d(CH_2)_5Tyr(Et)$ VAVP. Acta Med. Hung. **43:** 333–339, 1986.

LÁSZLÓ, F. A., CSÁTI, S., AND BALÁSPIRI, L.: Effect of the vasopressin antagonist $d(CH_2)_5Tyr(Et)$ VAVP on the antidiuretic action of exogenous and endogenous vasopressin. Acta Endocrinol. **106:** 52–55, 1984a.

LÁSZLÓ, F. A., CSÁTI, S., AND BALÁSPIRI, L.: Prevention of hyponatraemia and cerebral oedema by the vasopressin antagonist $d(CH_2)_5Tyr(Et)$ VAVP in rats treated with pitressin tannate. Acta Endocrinol. **106:** 56–60, 1984b.

LÁSZLÓ, F. A., CSÁTI, S., BALÁSPIRI, L., AND MANNING, M.: Effect of the vasopressin antagonist $d(CH_2)_5Tyr(Et)$ VAVP on diuresis in rat. Acta Med. Hung. **41:** 56–73, 1984c.

LÁSZLÓ, F. A., JANÁKY, T., JULESZ, J., KÁRTESZI, M., MAKARA, G. B., AND STARK, E.: Effects of arginine-8-vasopressin and 1-deamino-8-D-arginine vasopressin on ACTH secretion in rats. Endocrinol. Exp. (Brastil) **17:** 133–136, 1983.

LÁSZLÓ, F. A., LEPRÁN I., AND BALÁSPIRI, L.: Cardiovascular effects of vasopressin agonists and antagonist in rats. Exp. Clin. Endocrinol. **7:** 237–241, 1988.

LAUNAY, J. M., VITTET, D., VIDAUD, M., RONDOT, A., MATHIEU, N., LALAU-KERALY, C., CANTAU, B., AND CHEVILLARD, C.: V_{1a} vasopressin specific receptors on human platelets: potentiation by ADP and epinephrine and evidence for homologous down-regulation. Thromb. Res. **45:** 323–331, 1987.

LAW, H. D., AND DU VIGNEAUD, V.: Synthesis of 2-p-methoxyphenyl-alanine oxytocin (O-methyl-oxytocin) and some observations on its pharmacological behavior. J. Am. Chem. Soc. **82:** 4579–4581, 1960.

LAYCOCK, J. F., PENN, W., SHIRLEY, D. G., AND WALTERS, S. J.: The role of vasopressin in blood pressure regulation immediately following acute haemorrhage in rats. J. Physiol. (Lond.) **296:** 267–275, 1979.

LEE-KWON, W. J., SHARE, L., CROFTON, J. T., AND SHADE, R. E.: Vasopressin in the rat with partial nephrectomy-salt hypertension. Clin. Exp. Hypertens. **3:** 281–297, 1981.

LEUNG, F. W., ITOH, M., HIRABAYASHI, K., AND GUTH, P. H.: Role of blood flow in gastric and duodenal mucosal injury in the rat. Gastroenterology **88:** 281–289, 1985.

LIARD, J.-F.: Vasopressin in cardiovascular control: role of circulating vasopressin. Clin. Sci. **67:** 473–481, 1984.

LIARD, J.-F.: Effects of arginine vasopressin on regional circulations In Vasopressin, ed. by R. W. Schrier, pp. 59–67, Raven Press, New York, 1985.

LIARD, J.-F.: Cardiovascular effects associated with antidiuretic activity of vasopressin after blockade of its vasoconstrictor action in dehydrated dogs. Circ. Res. **58:** 631–640, 1986.
LIARD, J.-F.: Antidiuretic agonists increase cardiac output and decrease vascular resistance in conscious dogs. J. Hypertens., in press, 1990.
LIARD, J.-F., DERIAZ, O., SCHELLING, P., AND THIBONNIER, M.: Cardiac output distribution during vasopressin infusion or dehydration in conscious dogs. Am. J. Physiol. **243:** H663–H669, 1982.
LINKOLA, J., YLIKAHRI, R., FYHRQUIST, F., AND VALLENIUS, M.: Plasma vasopressin in ethanol intoxication and hangover. Acta Physiol. Scand. **104:** 180–187, 1978.
LINTON, E. A., GILLIES, G. E., AND LOWRY, P.J.: Ovine corticotropin-releasing factor and vasopressin: antibody-quenching studies on hypothalamic extracts of normal and Brattleboro rats. Endocrinology **113:** 1878–1883, 1983.
LINTON, E. A., TILDERS, F. J. H., HODGKINSON, S., BERKENBOSCH, F., VERMES, I., AND LOWRY, P. J.: Stress-induced secretion of adrenocorticotropin in rats is inhibited by administration of antisera to ovine corticotropin releasing factor and vasopressin. Endocrinology **116:** 966–970, 1985.
LIVON, C.: Secretions internes, glandes hypertensives. Compt. Rend. Soc. Biol. (Paris) **50:** 98, 1898.
LLOYD, S., AND PICKFORD, M.: The action of posterior pituitary hormones and oestrogens on the vascular system of the rat. J. Physiol. (Lond.) **155:** 161–174, 1961.
LLOYD, S., AND PICKFORD, M.: Effects of oestrogens and sympathetic denervation on response to oxytocin of blood vessels in hind limb of dog. J. Physiol. (Lond.) **163:** 362–371, 1962.
LOWBRIDGE, J., MANNING, M., HALDAR, J., AND SAWYER, W. H.: [1-beta-mercapto-beta, beta, cyclopentamethylenepropionic acid, 4-valine-8D-arginine] vasopressin, a potent and selective inhibitor of the vasopressor response to arginine vasopressin. J. Med. Chem. **21:** 313–315, 1978.
MAGGI, M., GENAZZANI, A. D., GIANNINI, S., TORRISI, C., BALDI, E., DI TOMASSO, M., MUNSON, P. J., ROBBARD, D., AND SERIO, M.: Vasopressin and oxytocin receptors in vagina, myometrium, and oviduct of rabbits. Endocrinology **122:** 2970–2980, 1988.
MAGGI, M., MALOWZOWSKI, S., KASSIS, S., GUARDABASSO, V., AND RODBARD, D.: Identification and characterization of two classes of receptors for oxytocin and vasopressin in porcine tunica albuginea, epididymis and vas deferens. Endocrinology **120:** 986–994, 1987.
MAGNUS, R., AND SCHAEFER, E. A.: The action of pituitary extracts upon kidney (abstr.). J. Physiol. **27:** IX, 1901.
MAH, S. C., FARAG, G. S., PHILLIPS, M. E., AND HOFBAUER, K. G.: Chronic blockade of vascular and tubular receptors of arginine-vasopressin (AVP) in rats (abstr.). Naunyn Schmiedebergs Arch. Phamacol. **332:** R42, 1986.
MAH, S. C., WHITEBREAD, S. E., DE GASPARO, M., AND HOFBAUER, K. G.: [^{3}H] AVP binding to rat renal tubular receptor during long-term treatment with an antagonist of arginine vasopressin. Peptides **9:** 595–600, 1988.
MALAYAN, S. A., RAMSEY, D. J., KEIL, L. C., AND REID, J. A.: Effects of increases in plasma vasopressin concentration on plasma renin activity, blood pressure, heart rate and plasma corticosteroid concentration in conscious dogs. Endocrinology **107:** 1899–1904, 1980.
MANNING, M.: Synthesis by the Merrifield method of a protected monopeptide amide with the amino acid sequence of oxytocin. J. Am. Chem. Soc. **90:** 1348–1349, 1968.
MANNING, M., BANKOWSKI, K., AND SAWYER, W. H.: Selective agonists and antagonists of vasopressin. *In* Vasopressin, ed. by D. M. Gash and G. J. Boer, pp. 335–368, Plenum Press, New York, 1987a.
MANNING, M., GRZONKA, Z., AND SAWYER, W. H.: Synthesis of posterior pituitary hormones and hormone analogues. *In* The Pituitary, ed, by C. Beardwell and G. Robertson, pp. 265–296, Butterworth, London, 1981a.
MANNING, M., KLIS, W. A., KRUSZYNSKI, M., PRZYBYLSKI, J. P., OLMA, A., WO, N. C., PELTON, G. H., AND SAWYER, W. H.: Novel linear antagonists of the antidiuretic (V_2) and vasopressor (V_1) responses to vasopressin. Int. J. Pept. Protein. Res. **32:** 455–467, 1988.
MANNING, M., KLIS, W. A., OLMA, A., SETO, J., AND SAWYER, W. H.: Design of more potent and selective antagonists of the antidiuretic responses to arginine vasopressin. J. Med. Chem. **25:** 414–419, 1982a.
MANNING, M., LAMMEK, B., BANKOWSKI, K., SETO, J., AND SAWYER, W. H.: Synthesis and some of the pharmacological properties of 18 potent O-alkyltyrosine substituted antagonists of the vasopressor responses to arginine vasopressin. J. Med. Chem. **28:** 1485–1491, 1985.
MANNING, M., LAMMEK, B., KOLODZIEJCZYK, A., SETO, J., AND SAWYER, W. H.: Synthetic antagonists of *in vivo* antidiuretic and vasopressor responses to arginine vasopressin. J. Med. Chem. **24:** 701–706, 1981b.
MANNING, M., LAMMEK, B., KRUSZYNSKI, M., SETO, J., AND SAWYER, W. H.: Design of potent and selective antagonists to the vasopressor responses to arginine vasopressin. J. Med. Chem. **25:** 408–414, 1982b.
MANNING, M., LOWBRIDGE, J., STIER, T. C. JR., HOLDAR, J., AND SAWYER, W. H.: [1-deaminopenicillamine, 4-valine] -8D-arginine-vasopressin, a highly potent inhibitor of the vasopressor response to arginine-vasopressin. J. Med. Chem. **20:** 1228–1230, 1977.
MANNING, M., MISICKA, A., OLMA, A., KLIS, W. A., BANKOWSKI, K., NAWROCKA, E., KRUSZYNSKI, M., KOLODZIEJCZYK, A., CHENG, L. L., SETO, J., WO, N. C., AND SAWYER, W. H.: C-terminal deletions in agonistic and antagonistic analogs of vasopressin that improve their specificities for antidiuretic (V_2) and vasopressor (V_1) receptors. J. Med. Chem. **30:** 2245–2252, 1987b.
MANNING, M., NAWROCKA, E., MISICKA, A., KLIS, W. A., OLMA, A., KRUSZYNSKI, M., KOLODZIEJCZYK, A. M., BANKOWSKI, K., SETO, J., AND SAWYER, W. H.: Design and synthesis of antagonists of vasopressin possessing enhanced anti-antidiuretic potencies and selectivities. *In* Peptides, Proceedings of the 18th European Peptide Symposium, Djuroneset, Sweden, 1984, ed. by U. Ragnarsson, pp. 401–405, Almquist and Wiksell, Upsala, Sweden, 1984a.
MANNING, M., NAWROCKA, E., MISICKA., A., OLMA, A., AND KLIS, W. A.: Potent and selective antagonists of the antidiuretic responses to arginine-vasopressin based on modifications of [1-(beta-mercapto-beta, beta cyclopentamethylene-propionic acid), 2-D-isoleucine, 4-valine] arginine vasopressin at position 4. J. Med. Chem. **27:** 423–429, 1984b.
MANNING, M., OLMA, A., KLIS, W. A., KOLODZIEJCZYK, A., NAWROCKA, E., MISICKA, A., SATO, J., AND SAWYER, W. H.: Carboxy-terminus of vasopressin required for activity but not binding. Nature (Lond.) **308:** 652–653, 1984c.
MANNING, M., OLMA, A., KLIS, W. A., KOLODZIEJCZYK, A. M., SETO, J., AND SAWYER, W. H.: Design of more potent antagonists of the antidiuretic responses to arginine vasopressin. J. Med. Chem. **25:** 45–50, 1982c.
MANNING, M., PRZYBYLSKI, J. P., LAMMEK, B., GRZONKA, Z., OLMA, A., BANKOWSKI, K., MISICKA, A., KRUSZYNSKI, M., AND SAWYER, W. H.: Surprising findings with some deletion-modified selective V_2 antagonists of arginine vasopressin (AVP). *In* Peptides, ed. by D. Theodoropoulos, pp. 459–463, de Gruyter, Berlin, Germany, 1987c.
MANNING, M., PRZYBYLSKI, J. P., OLMA, A., KLIS, W. A., KRUSZYNSKI, M., WO, N. C., PELTON, G. H., AND SAWYER, W. H.: No requirement of cyclic conformation for binding of antagonists to vasopressin receptors. Nature (Lond.) **329:** 839–840, 1987d.
MANNING, M., AND SAWYER, W. H.: Invited editorial: antagonists of vasopressor and antidiuretic responses to arginine vasopressin. Ann. Intern. Med. **96:** 520–522, 1982.
MANNING, M., AND SAWYER, W. H.: Design of potent and selective *in vivo* antagonists of the neurohypophyseal peptides Prog. Brain Res. **60:** 367–382, 1983.
MANNING, M., AND SAWYER, W. H.: The development of selective agonists and antagonists of vasopressin. *In* Vasopressin, ed. by R. W. Schrier, pp. 131–144, Raven Press, New York, 1985.
MANNING, M., AND SAWYER, W. H.: Discovery, development and some uses of vasopressin and oxytocin antagonists. J. Lab. Clin. Med. **114:** 617–632, 1989.
MANNUCCI, P. M., PARETI, F. J., RUGGERI, Z. M., AND CAPITANIO, A.: 1-deamino-8D-arginine vasopressin. A new pharmacological approach to the management of haemophilia and von Willebrand's disease. Lancet **1:** 869, 1977.
MARTINI, L., AND MORPURGO, C.: Neurohumoral control of release of adrenocorticotrophic hormone. Nature (Lond.) **175:** 1127–1128, 1955.
MATSUGUCHI, H., AND SCHMID, P. G.: Acute interaction of vasopressin and neurogenic mechanisms in DOC-salt hypertension. Am. J. Physiol. **242:** H37–H43, 1982.
MATUK, F., AND KALYANARAMAN, K.: Syndrome of inappropriate secretion of antidiuretic hormone in patients treated with psychotherapeutic drugs. Arch. Neurol. **134:** 374–375, 1977.
MAZZIA, V. D. B., MCKENNA, J. M., GYURE, L., AND HERSHEY, S. G.: Influence of a synthetic analogue of vasopressin on the microcirculation and survival in shock. Fed. Proc. **23:** 539, 1964.
MCCANN, S. M.: The ACTH-releasing activity of extracts of the posterior lobe of the pituitary *in vivo*. Endocrinology **60:** 664–676, 1957.
MCCANN, S. M., AUTUNES-RODRIGUES, J., NALLAR, R., AND VALTIN, H.: Pituitary-adrenal function in the absence of vasopressin. Endocrinology **79:** 1058–1064, 1966.
MCNEILL, J. R.: Role of vasopressin and angiotensin in response of splanchnic resistance vessels to hemorrhage. Adv. Exp. Med. Biol. **23:** 127–144, 1972.
MCNEILL, J. R.: Intestinal vasoconstriction following diuretic-induced volume depletion: role of angiotensin and vasopressin. Can. J. Physiol. Pharmacol. **52:** 829–839, 1974.
MCNEILL, J. R., STARK, R. D., AND GREENWAY, C. V.: Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. Am. J. Physiol. **219:** 1342–1347, 1970.
MEIDAN, R., AND HSUEH, A. J. W.: Identification, characterization of arginine vasopressin receptors in the rat testis. Endocrinology **116:** 416–423, 1985.
MELIN, P., TROJNAR, J., JOHANSSON, B., VILHARDT, H., AND AKERLUND, M.: Synthetic antagonists of the myometrial response to vasopressin and oxytocin. J. Endocrinol. **111:** 125–131, 1986.
MERRIFIELD, R. B.: Solid phase synthesis. I. The synthesis of a tetrapeptide. J. Am. Chem. Soc. **85:** 2149–2154, 1963.
MICHELL, R. H., KIRK, C. J., AND BILLAH, M. M.: Hormonal stimulation of phosphatidylinositol breakdown with particular reference to the hepatic effects of vasopressin. Biochem. Soc. Trans. **7:** 861–865, 1979.
MILLER, P. D., LINAS, S. L., AND SCHRIER, R. W.: Plasma demeclocycline levels and nephrotoxicity: correlation in hyponatremic cirrhotic patients. JAMA **243:** 2513–2515, 1980.
MILLER, M., MOSES, A. N., AND RAO, K. J.: Water intoxication and thioridazine. Ann. Intern. Med. **82:** 852, 1973.
MOHRING, J., GLANZER, K., MACIEL, J. A., JR., DUSING, R., KRAMER, H. J., ARBOGAST, R., AND KOCH-WESER, J.: Greatly enhanced pressor response to antidiuretic hormone in patients with impaired cardiovascular reflexes due to idiopathic orthostatic hypotension. J. Cardiovasc. Pharmacol. **2:** 367–376, 1980.
MOHRING, B., AND MOHRING, J.: Plasma ADH in normal Long-Evans rats and in Long-Evans rats heterozygous and homozygous for hypothalamic diabetes insipidus. Life Sci. **17:** 1307–1314, 1975.
MONTANI, J. P., LIARD, J.-F., SCHOUN, J., AND MOHRING, J.: Hemodynamic effects of exogenous and endogenous vasopressin at low plasma concentration in conscious dogs. Circ. Res. **47:** 346–355, 1980.
MOODY, E. G., MCGREEVY, J., ZALEWSKY, C., CHEUNG, L. Y., AND SIMONS, M.

The cytoprotective effect of mucosal blood flow in experimental erosive gastritis. Acta Physiol. Scand. **35** (special suppl): 35–43, 1978.

MOORE, M. L., ALBRIGHTSON, C., BRICKSON, B., BRYAN, H. G., CALDWELL, N., CALLAHAN, J. F., FOSTER, J., KINTER, L. B., NEWLANDER, K. A., SCHMIDT, D. B., SORENSON, E., STASSEN, F. L., YIM, N. C. F., AND HUFFMAN, W. F.: Dicarba vasopressin antagonist analogues exhibit reduced *in vivo* agonist activity. J. Med. Chem. **31:** 1487–1489, 1988.

MOREL, F., CHABARDÈS, D., AND IMBERT-TEBOUL, M.: Heterogeneity of hormone control in the distal nephron. *In* Proceedings of the VIIth International Congress of Nephrology, pp. 209–216, Athens, Greece, 1978.

MOREL, F., CHABARDÈS, D., AND IMBERT-TEBOUL, M.: Effect of catecolamines on adenylate cyclase activity along the rat nephron (abstr.). Upsala J. Med. Sci. (Suppl.) **26:** 53, 1979.

MOREL, F., CHABARDÈS, D., IMBERT-TEBOUL, M., LE BOUFFANT, F., HUS-CITHAREL, A., AND MONTÉGUT, M.: Multiple hormonal control of adenylate cyclase in distal segments of the rat kidney. Kidney Int. **21** (suppl. 11): S55–S62, 1982.

MOREL, F., IMBERT-TEBOUL, M., AND CHABARDÈS, D.: Distribution of hormone-dependent adenylate cyclase in the nephron and its physiological significance. Annu. Rev. Physiol. **43:** 569–581, 1981.

MOREL, F., IMBERT-TEBOUL, M., AND CHABARDÈS, D.: Receptors to vasopressin and other hormones in the mammalian kidney. Kidney Int. **31:** 512–520, 1987.

MORMÈDE, P.: The vasopressin receptor antagonist dPTyr(Me) AVP does not prevent stress-induced ACTH and corticosterone release. Nature (Lond.) **302:** 345–346, 1983.

MORTON, J. J., PADFIELD, P. L., AND FORSLING, M. L.: A radioimmunoassay for plasma arginine vasopressin in man and dog: application to physiological and pathological states. J. Endocrinol. **65:** 411–424, 1975.

MURPHY, F. J., AND ZELMAN, S.: Water metabolism and the psychiatric patient. J. Urol. **92:** 60–63, 1964.

NAKANO, J.: Cardiovascular responses to neurohypophyseal hormones. *In* Handbook of Physiology, section 7: Endocrinology, vol. IV: The Pituitary Gland and Its Neuroendocrine Control, part 1, ed. by R. O. Greep and E. B. Astwood, pp. 395–442, American Physiological Society, Washington, D. C., 1974.

Narins, R., Jones, E. R., Stom, M. C., Rudnick, M. R., and Bastl, C. P.: Diagnostic strategies in disorders of fluid, electrolytes and acid-base homeostasis. Am. J. Med. **72:** 496–520, 1982.

NICOD, P., WAEBER, B., BUSSIEN, J. P., GOY, J. J., TURINI, G., NUSSBERGER, J., HOFBAUER, K. G., AND BRUNNER, H. R.: Acute hemodynamic effect of a vascular antagonist of vasopressin in patients with congestive heart failure. Am. J. Cardiol. **55:** 1043–1047, 1985.

OHLSTEIN, E. H., AND BERKOWITZ, B. A.: Human vascular vasopressin receptors: analysis with selective vasopressin receptor antagonists. J. Pharmacol. Exp. Ther. **239:** 737–741, 1986.

OKUNO, T., WINTERNITZ, S. R., LINDHEIMER, M. D., AND OPARIL, S.: Central catecholamine depletion, vasopressin, and blood pressure in the DOCA/NaCl rat. Am. J. Physiol. **244:** H807–H813, 1983.

OLIVER, H., AND SCHAEFER, E. A.: On the physiological action of extracts of the pituitary body and certain other glandular organs. J. Physiol. (Lond.) **18:** 277–279. 1895.

OMACHI, R. S., ROBBIE, D. E., HANDLER, J. S., AND ORLOFF, J.: Effects of ADH and other agents on cyclic AMP accumulation in toad bladder epithelium. Am. J. Physiol. **226:** 1152–1157, 1974.

ORLOFF, J., AND HANDLER, J. S.: The similarity of effects of vasopressin, adenosine-3′,5′-phosphate (cyclic AMP) and theophylline on the toad bladder. J. Clin. Invest. **41:** 702–709, 1962.

ORLOFF, J., HANDLER, J. S., AND BERGSTROM, S.: Effect of prostaglandin (PGE_1) on the permeability of response of toad bladder to vasopressin, theophylline and adenosine3′,5′-monophosphate. Nature (Lond.) **205:** 397–398, 1965.

OSBORN, J. W., JR., WEBB, R. L., AND COWLEY, A. W., JR.: Hemodynamic and autonomic effects of arginine vasopressin compared to angiotensin II in conscious rats. Am. J. Physiol. **252** (Heart Circ. Physiol. 21): H628–H637, 1987.

PALLER, M. S., AND LINAS, S. L.: Role of vasopressin in support of blood pressure in potassium deficient rats. Kidney Int. **24:** 342–347, 1983.

PANG, C. C. Y.: Effect of vasopressin antagonist and saralasin on regional blood flow following hemorrhage. Am. J. Physiol. **245:** H749–H755, 1983.

PANG, C. C. Y., MCNEILL, J. R., WILCOX, W. C., MANNING, M., AND SAWYER, W. H.: [l-Deaminopenicillamine,4-Valine,8-D arginine]-vasopressin antagonizes the mesenteric vasoconstrictor response to arginine vasopressin in cats. Proc. Soc. Exp. Biol. Med. **161:** 41–43, 1979.

PEARLMUTTER, A. F., RAPINO, E., AND SAFFRAN, M.: A semi-automated *in vitro* assay for CRF: activities of peptides related to oxytocin and vasopressin. Neuroendocrinology **15:** 106–119, 1974.

PEARLMUTTER, A. F., SZKRYBALO, M., AND PETTIBONE, G.: Specific arginine vasopressin binding in particulate membrane from rat aorta. Peptides **6:** 427–431, 1985.

PECK, V., AND SHENKMAN, L.: Haloperidol-induced syndrome of inappropriate secretion of antidiuretic hormone. Clin. Pharmacol. Ther. **20:** 442–444, 1979.

PENIT, J., FAURE, M., AND JARD, S.: Vasopressin and angiotensin II receptor in rat aortic smooth muscle cells in culture. Am. J. Physiol. **244:** E72–E82, 1983.

PHILLIPS, P. A., ABRAHAMS, J. M., KELLY, J., PAXINOS, G., GRZONKA, Z., MENDELSOHN, F. A. O., AND JOHNSTON, C. I.: Localization of vasopressin binding sites in rat brain by in vitro autoradiography using a radioiodinated V_1 receptor antagonist. Neurosciences **27:** 749–755, 1988.

PITTMAN, Q. J., AND LAWRENCE, D.: Descending hypothalamic pathways; electrophysiological investigations of their possible functions. *In* Neuroendocrinology of Vasopressin, Corticoliberin and Opiomelanocortins, ed. by A. J. Baertschi and J. J. Dreifuss, pp. 167–176, Academic Press, London, 1982.

PLETSCHER, A., ERNE, P., BÜRGISSER, E., AND FERRACIN, F.: Activation of human blood platelets by arginine vasopressin: role of bivalent cations. Mol. Pharmacol. **28:** 508–514, 1985.

PORTANOVA, R., AND SAYERS, G.: Isolated pituitary cells: CRF-like activity of neurohypophysial and related polypeptides. Proc. Soc. Exp. Biol. Med. **143:** 661–666, 1973.

QUILLEN, E. W., JR., AND COWLEY, A. W., JR.: Influence of volume changes on osmolality-vasopressin relationship in conscious dogs. Am. J. Physiol. **244:** H73–H79, 1983.

RABITO, S. F., CARRETERO, O. A., AND SCICLI, A. G.: Evidence against a role of vasopressin in the maintenance of high blood pressure in mineralocorticoid and renovascular hypertension. Hypertension **3:** 34–38, 1981.

RAGGENBASS, M., DUBOIS-DAUPHIN, M., TRIBOLLET, E., AND DREIFUSS, J. J.: Direct excitatory action of vasopressin in the lateral septum of the rat brain. Brain Res. **459:** 60–65, 1988.

RAGGENBASS, M., TRIBOLLET, E., AND DREIFUSS, J. J.: Electrophysiological and autoradiographical evidence of V_1 vasopressin receptors in the lateral septum of the rat brain. Proc. Natl. Acad. Sci. USA **84:** 7778–7782, 1987.

RAJERISON, R., MARCHETTI, J., ROY, C., BOCKAERT, J., AND JARD, S.: The vasopressin-sensitive adenylate cyclase of the rat kidney: effect of adrenalectomy and corticosteroids on hormonal receptor/enzyme coupling. J. Biol. Chem. **249:** 6390–6400, 1974.

RAJERISON, R. M., BUTLEN, D., AND JARD, S.: Effects of *in vivo* treatment with vasopressin and analogues on renal adenylate cyclase responsiveness to vasopressin stimulation *in vitro*. Endocrinology **101:** 1–12, 1977.

RASCHER, W., LANG, R. E., GANTEN, D., MEFFLE, H., TAUBITZ, M., UNGER, T., AND GROSS, F.: Vasopressin in deoxycorticosterone acetate hypertension of rats: a hemodynamic analysis. J. Cardiovasc. Pharmacol. **5:** 418–425, 1983.

RASCHER, W., MEFFLE, H., AND GROSS, F.: Haemodynamic effects of arginine vasopressin in conscious water-deprived rats. Am. J. Physiol. **249:** H29–H33, 1985.

RASKIND, M. A.: Psychosis, polydipsia, and water intoxication. Arch. Gen. Psychiatry **30:** 112–114, 1974.

RASKIND, M. A., ORENSTEIN, H., AND CHRISTOPHER, T. G.: Acute psychosis, increased water ingestion, and inappropriate antidiuretic hormone secretion. Am. J. Psychiatry **132:** 907–910, 1975.

RASKIND, M. A., WEITZMAN, R. E., ORENSTEIN, H., FISHER, D. A., AND COURTNEY, N.: Is antidiuretic hormone elevated in psychosis? A pilot study. Biol. Psychiatry **13:** 385–390, 1978.

REEDER, R. F., NATTIE, E. E., AND NORTH, W. G.: Effect of vasopressin on cold-induced brain edema in cats. J. Neurosurg. **64:** 941–950, 1986.

RIBEIRO, A., MULINARI, R., GAVRAS, I., KOHLMANN, O., RAMOS, O., AND GAVRAS, H.: Sequential elimination of pressor mechaniams in severe hypertension in humans. Hypertension **8** (suppl. I): I169–I173, 1986.

RIEGGER, G. J. A., LIEBAU, G., AND KOCHSIEK, K.: Antidiuretic hormone in congestive heart failure. Am. J. Med. **72:** 49–52, 1982.

RITCHIE, W. P.: Acute gastric mucosal damage induced by bile salts, acid and ischemia. Gastroenterology **68:** 699–707, 1975.

RIVIER, C., RIVIER, J., MORMEDE, P., AND VALE, W.: Studies of the nature of the interaction between vasopressin and corticotropin releasing factor on adrenocorticotropin release in the rat. Endocrinology **115:** 882–886, 1984.

RIVIER, C., AND VALE, W.: Interaction of corticotropin releasing factor (CRF) and arginine vasopressin (AVP) on adrenocorticotropin secretion *in vivo*. Endocrinology **113:** 939–942, 1983a.

RIVIER, C., AND VALE, W.: Modulation of stress-induced ACTH release by corticotropin-releasing factor, catecholamines and vasopressin. Nature (Lond.) **305:** 325–327, 1983b.

RIVIER, C., AND VALE, W.: Neuroendocrine interaction between corticotropin releasing factor and vasopressin on adrenocorticotropic hormone secretion in the rat. *In* Vasopressin, ed. by R. W. Schrier, pp. 181–188, Raven Press, New York, 1985.

ROBERT, A.: Cytoprotection by prostaglandins. Gastroenterology **77:** 761–767, 1979.

ROBERT, A., GUTH, P. H., SCHMIDT, K. L., AND MILLER, T. A.: Response to an editorial on gastric cytoprotection. Gastroenterology **96:** 548–554, 1989.

ROBERTSON, G. L.: The regulation of vasopressin function in health and disease. Recent Prog. Horm. Res. **33:** 333–385, 1977.

ROBERTSON, G. L., MAHR, E. A., ATHAR, S., AND SINHA, T.: Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. J. Clin. Invest. **52:** 2340–2352, 1973.

ROCHA E SILVA, M., JR., AND ROSENBERG, M.: The release of vasopressin in response to haemorrhage and its role in the mechanism of blood pressure regulation. J. Physiol. (Lond.) **202:** 535–557, 1969.

ROCKHOLD, R. W., SHARE, L., CROFTON, J. T., AND BROOKS, D. P.: Cardiovascular response to vasopressin vasopressor antagonist administration during water deprivation in the rat. Neuroendocrinology **38:** 139–144, 1984.

RONDEAU, E., DE LIMA, J., CAILLENS, H., ARDAILLA, R., VAHANIAN, A., AND ACAR, T.: High plasma antidiuretic hormone in patients with cardiac failure: influence of age. Miner. Electrolyte Metab. **8:** 267–274, 1982.

ROSENBERG, G. A., KYNER, W., T., FENSTERMACHER, J. D. AND PATLAK, C. S.: Effect of vasopressin on ependymal and capillary permeability to tritiated water in cat. Am. J. Physiol. **251:** (Pt 2): F485–489, 1986.

RUNDGREN, M., OLSSON, K., APPELGREN, B., AND FYHRQUIST, F.: Effects of hemorrhage on vasopressin secretion and arterial blood pressure during experimental diabetes insipidus in goats. Acta Physiol. Scand. **116:** 57–65, 1982.

SAAMELI, K.: The circulatory actions of the neurohypophysial hormones and similar polypeptides. *In* Handbook of Experimental Pharmacology, vol. 23, ed. by B. Berde, pp. 545–611, Springer-Verlag, Heidelberg, Germany, 1968.

SACHS, H., SHARE, L., OSINCHAK, J., AND CARPI, A.: Capacity of the neurohypophysis to release vasopressin. Endocrinology 81: 755–770, 1967.
SAFFRAN, M., AND SCHALLY, A. V.: Release of corticotrophin by anterior pituitary tissue *in vitro*. Can. J. Biochem. Physiol. 33: 408–415, 1955.
SAITO, T., AND YAJIMA, Y.: Development of DOCA-salt hypertension in the Brattleboro rat. Ann. NY Acad. Sci. 309–318, 1982.
SAWYER, W. H.: Differences in antidiuretic responses of rats to intravenous administration of lysine and arginine vasopressins. Endocrinology 63: 694–698, 1958.
SAWYER, W. H.: Neurohypophysial hormones. Pharmacol. Rev. 13: 225–227, 1971.
SAWYER, W. H.: The development of potent and specific vasopressin antagonists. Kidney Int. 26 (suppl.): S34–S37, 1988.
SAWYER, W. H., ACOSTA, M., BALASPIRI, L., JUDD, J., AND MANNING, M.: Structural changes in the arginine vasopressin molecule that enhance antidiuratic activity and specificity. Endocrinology 94: 1106–1115, 1974a.
SAWYER, W. H., ACOSTA, M., AND MANNING, M.: Structural changes in the arginine vasopressin molecule that prolong its antidiuretic action. Endocrinology 95: 140–149, 1974b.
SAWYER, W. H., BANKOWSZKI, K., MISICKA, A., NAWROCKA, E., KRUSZYNSKI, M., STOEV, S., KLIS, W. A., PRZYBYLSKI, J. P., AND MANNING, M.: Potent V_2 antagonists with structural changes at their C-terminals. Peptides 9: 157–163, 1988.
SAWYER, W. H., GRZONKA, Z., AND MANNING, M.: Neurohypophysial peptides: design of tissue specific agonists and antagonists. Mol. Cell. Endocrinol. 22: 117–136, 1981a.
SAWYER, W. H., AND MANNING, M.: The use of antagonists of vasopressin in studies of its physiological functions. Fed. Proc. 44: 78–80, 1985.
SAWYER, W. H., AND MANNING, M.: The development of potent and specific vasopressin antagonists. Kidney Int. 34 (suppl. 26): S34–S37, 1988.
SAWYER, W. H., PANG, P. K. T., SETO, J., MCENROE, M., LAMMEK, B., AND MANNING, M.: Vasopressin analogs that antagonize antidiuretic responses by rats to the antidiuretic hormone. Science 212: 49–51, 1981b.
SCHAEFER, E. A., AND HERRING, P. T.: The action of pituitary extracts upon kidney. Phil. Trans. R. Soc. London (B) 199: 1, 1908.
SCHILD, H. O.: pA, a new scale of the measurement of drug antagonism. Br. J. Pharmacol. Chemother. 2: 189–206, 1947.
SCHMITT, S. L., TAYLOR, K., SCHMIDT, R., VAN ORDEN, D., AND WILLIAMSON, H. E.: The role of volume depletion, antidiuretic hormone and angiotensin II in the furosemide-induced decrease in mesenteric conductance in the dog. J. Pharmacol. Exp. Ther. 219: 407–414, 1981.
SCHRIER, R. W.: New treatments for hyponatraemia. N. Engl. J. Med. 298: 214–215, 1978.
SCHRIER, R. W.: Treatment of hyponatremia. N. Engl. J. Med. 312: 1121–1123, 1985.
SCHRIER, R. W., AND BICHET, D. G.: Osmotic and non-osmotic control of vasopressin release and the pathogenesis of impaired water excretion in adrenal, thyroid and edematous disorders. J. Lab. Clin. Med. 98: 1–15, 1981.
SCHRIER, R. W., AND KIM, J. K.: Vasopressin antagonists. *In* Diuretics, ed. by Puschett, J. B., pp. 56–63, Elsevier, Amsterdam, 1984.
SCHULZ, H., AND DU VIGNEAUD, V.: Synthesis of 1-L-penicillamine-oxytocin, 1-D-penicillamine-oxytocin, and 1-deaminopenicillamine-oxytocin, potent inhibitors of the oxytocin response of oxytocin. J. Med. Chem. 3: 647–650, 1966.
SCHUSTER, V. L., JACOBSON, H. R., AND KOKKO, J. P.: Interactions of lysyl-bradykinin and antidiuretic hormone in the rabbit cortical collecting tubule. J. Clin. Invest. 73: 1659–1667, 1984.
SCHWARTZ, J., KEIL, L. C., MASELLI, J., AND REID, I. A.: Role of vasopressin in blood pressure regulation during adrenal insufficiency. Endocrinology 112: 234–238, 1983.
SCHWARTZ, J., LIARD, J.-F., AND COWLEY, A. W., JR.: Cardiovascular actions of the antidiuretic activity of vasopressin. Am. J. Physiol. 249: 1001–1008, 1985a.
SCHWARTZ, J., LIARD, J.-F., OTT, C., AND COWLEY, A. W., JR.: Hemodynamic effects of neurohypophyseal peptides with antidiuretic activity in dogs. Am. J. Physiol. 249: H1001–H1008, 1985b.
SCHWARTZ, J., AND REID, I. A.: Effect of vasopressin blockade on blood pressure regulation during hemorrhage in conscious dogs. Endocrinology 109: 1778–1780, 1981.
SCHWARTZ, J., AND REID, I. A.: Role of vasopressin in blood pressure regulation in conscious water-deprived dogs. Am. J. Physiol. 244: R74–R77, 1983.
SCHWARTZ, M. J., AND KOKKO, J. P.: Urinary concentrating defect of adrenal insufficiency: permissive role of adrenal steroids on the hydroosmotic response across the rabbit collecting tubule. J. Clin. Invest. 66: 234–242, 1980.
SCHWARTZ, W. B., BENNETT, W., CURELOP, S., AND BARTTER, F. C.: A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am. J. Med. 23: 529–534, 1957.
SHARE, L.: Role of cardiovascular receptors in the control of ADH release. Cardiology 61 (suppl.): 51, 1976.
SHARE, L., AND CROFTON, J. T.: The role of vasopressin in hypertension. Fed. Proc. 43: 103–106, 1984.
SHIMAZU, T., AND AMAKAWA, A.: Regulation of glycogen metabolism in liver by the autonomic nervous system. VI. Possible mechanism of phosphorylase activation by the splanchnic nerve. Biochim. Biophys. Acta 385: 242–256, 1975.
SILEN, W.: What is cytoprotection of the gastric mucosa? Gastroenterology 94: 232–235, 1988.
SKOWSKY, W. R., AND KIKUCHI, T.: The role of vasopressin in the impaired water excretion of myxoedema. Am. J. Med. 64: 613–622, 1978.
SKOWSKY, W. R., ROSENBLOOM, A. A., AND FISHER, D. A.: Radioimmunoassay measurement of arginine vasopressin in serum: Development and application. J. Clin. Endocrinol. Metab. 38: 278–287, 1974.
SMELIK, P. G., GAARENSTROOM, J. H., KONIJNENDIJK, W., AND DE WIED, D.: Evaluation of the role of the posterior lobe of the hypophysis in the reflex secretion of corticotrophin. Acta Physiol. Pharmacol. 11: 20–23, 1962.
SMITH, W. O., AND CLARK, M. L.: Self-induced water intoxication in schizophrenic patients. Am. J. Psychiatry 137: 1055–1060, 1980.
STARK, R. D., MCNEILL, J. R., AND GREENWAY, C. Y.: Sympathetic and hypophyseal roles in the splenic response to hemorrhage. Am. J. Physiol. 220: 837–840, 1971.
STARLING, E. H., AND VERNEY, E. B.: The secretion of urine as studied on the isolated kidney. Proc. R. Soc. Lond. (Biol.) 97: 321–363, 1924.
STASSEN, F. L., BERKOWITZ, B. B., HUFFMAN, W. F., WIEBELHAUS, V.-D., AND KINTER, L. B.: Molecular pharmacology of aquaretic agents *In* Diuretics, ed. by Puschet, J. R., pp. 64–71, Elsevier, Amsterdam, 1984.
STASSEN, F. L., BRYAN, W., GROSS, M., KAVANAUGH, B., SHUE, D., SULAT, L., WIEBELHAUS, V. D., YIM, N., AND KINTER, L. B.: Critical differences between species *in vivo* and in vitro renal responses to antidiuretic hormone antagonists. Progr. Brain Res. 60: 395–403, 1983.
STASSEN, F. L., ERICKSON, R. W., HUFFMAN, W. F., STEFANKIEWICZ, J., SULAT, L., AND WIEBELHAUS, V. D.: Molecular mechanisms of novel antidiuretic antagonists: Analysis of the effects on vasopressin binding and adenylate cyclase activation in animals and human kidney. J. Pharmacol. Exp. Ther. 223: 50–54, 1982.
STASSEN, F. L., HECKMAN, G., SCHMIDT, D., PAPADOPOULOS, M. T., NAMBI, P., SARAU, H., AIYER, N., GELLAI, M., AND KINTER, L. B.: Oxytocin induces a transient increase in cytosolic free Ca in renal tubular epithelial cells. Mol. Pharmacol. 33: 218–224, 1988.
STASSEN, F. L., HECKMAN, G. D., SCHMIDT, D. B., STEFANKIEWICZ, J., SULAT, L., HUFFMAN, W. F., MOORE, M. M., AND KINTER, L. B.: Actions of vasopressin antagonists: molecular mechanisms. *In* Vasopressin, ed. by R. W. Schrier, pp. 145–154, Raven Press, New York, 1985.
ST.-LOUIS, J., AND SCHIFFRIN, E. L.: Biological action and binding sites for vasopressin on the mesenteric artery from normal and sodium-depleted rats. Life Sci. 35: 1489–1495, 1984.
STOFF, J. S., HANDLER, J. S., PRESTON, A. S., AND ORLOFF, J.: The effect of aldosterone on cyclic nucleotide phosphodiesterase activity in toad urinary bladder. Life Sci. 13: 545–552, 1973.
STUBBS, M., KIRK, C. J., AND HEMS, D. A.: Role of extracellular calcium in the action of vasopressin on hepatic glycogenolysis. FEBS Lett. 69: 199–202, 1976.
STÜRMER, E.: Bioassay procedures for neurohypophysial hormones and similar polypeptides. In Handbook of Experimental Pharmacology, vol. 23, ed. by B. Berde, pp. 130–189, Springer-Verlag, Berlin, 1968.
SZABO, S., TRIER, J. S., BROWN, A., AND SCHNOOR, J.: Early vascular injury and increased vascular permeability in gastric mucosal injury caused by ethanol in the rat. Gastroenterology 88: 228–236, 1985.
SZATALOWICZ, V. L., ARNOLD, P. E., CHAIMOVITZ, C., BICHET, D., BERL, T., AND SCHRIER, R. W.: Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. N. Engl. J. Med. 305: 263–266, 1981.
SZCZEPANSKA-SADOWSKA, E.: Hemodynamic effects of a moderate increase of the plasma vasopressin level in conscious dogs. Pflugers Arch. 338: 313–322, 1973.
SZCZEPANSKA-SADOWSKA, E., SOBOCINSKA, J., AND KOZLOWSKI, S.: Thirst impairment elicited by intaventricular administration of vasopressin antagonists. Peptides 8: 1003–1009, 1987.
TANAY, A., YUST, I., PERECENSCHI, G., ABRAMOV, A. L., AND AVIRAM, A.: Long-term treatment of the syndrome of inappropriate antidiuretic hormone secretion with phenytoin. Ann. Intern. Med. 90: 50–52, 1979.
TANG, A. H., AND HO, P. M.: A specific antagonist of vasopressin produced plasma hyperosmolality and reduced ischemic-induced cerebral edema in rats. Life Sci. 43: 399–403, 1988.
THIBONNIER, M.: Solubilization of human platelet vasopressin receptors. Life Sci. 40: 439–445, 1987a.
THIBONNIER, M.: The human platelet vasopressin receptor identification by direct ultraviolet photoaffinity labeling. J. Biol. Chem. 262: 10960–10964,. 1987b.
THIBONNIER, M.: Use of vasopressin antagonists in human diseases. Kidney Int. 34 (suppl. 26): S48–S51, 1988.
THIBONNIER, M., HINKO, A., AND PEARLMUTTER, A. F.: The human platelet vasopressin receptor and its intracellular messengers: key role of divalent cations. J. Cardiovasc. Pharmacol. 10: 24–29, 1987.
THIBONNIER, M., AND ROBERTS, J. M.: Characterization of human platelet vasopressin receptors. J. Clin. Invest. 76: 1857–1862, 1985.
THOMAS, M. E., OSMANI, A. H., AND SCRUTTON, M. C.: Some properties of the human platelet vasopressin receptor. Thromb. Res. 32: 557–566, 1983.
THURAU, L., AND LEVINE, D. Z.: The renal circulation. *In* The Kidney, Morphology, Biochemistry, Physiology, ed. by C. Rowiller and A. F. Muller, pp. 1–70, Academic Press, New York, 1971.
TORIKAI, S., WANG, M. S., KLEIN, K. L., AND KUROKAWA, K.: Adenylate cyclase and cell cyclic AMP of rat cortical thick ascending limb of Henle. Kidney Int. 20: 649–654, 1981.
TORRES, B. A., AND JOHNSON, H. M.: Arginine vasopressin (AVP) replacement of helper cell requirement in IFN-production. Evidence for a novel AVP receptor on mouse lymphocytes. J. Immunol. 140: 2179–2183, 1988.
TRIBOLLET, E., BARBERIS, C., DREIFUSS, J. J., AND JARD, S.: Autoradiographic localization of vasopressin and oxytocin binding sites in the rat kidney. Kidney Int. 33: 959–965, 1988a.

TRIBOLLET, E., BARBERIS, C., JARD, S., DUBOIS-DAUPHIN, M., AND DREIFUSS, J. J.: Localization and pharmacological characterization of high affinity binding sites for vasopressin and oxytocin in the rat brain by light microscopic autoradiography. Brain Res. **442:** 105–118, 1988b.

TURKELSON, C. M., THOMAS, C. R., ARIMURA, A., CHANG, D., CHANG, J. K., AND SHIMIZU, M.: In vitro potentiation of the activity of synthetic ovine corticotropin-releasing factor by arginine vasopressin. Peptides **1:** 111–113, 1982.

TURNER, R. A., PIERCE, J. G., AND DU VIGNEAUD, V.: The purification and the amino acid content of vasopressin preparation. J. Biol. Chem. **191:** 21, 1951.

UNDESSER, K. P., HASSER, E. M., HAYWOOD, J. R., JOHNSON, A. K., AND BISHOP, V. S.: Interactions of vasopressin with the area postrema in arterial baroreflex function in conscious rabbits. Circ. Res. **56:** 410–417, 1985.

UNGER, T., ROHMEISS, P., BECKER, H., GANTEN, D., LANG, R. E., AND PETTY, M.: Sympathetic activation following central vasopressin receptor stimulation in conscious rat. J. Hypertens. **2:** 25–27, 1984.

VALE, W., AND RIVIER, C.: Substances modulating the secretion of ACTH by cultured anterior pituitary cells. Fed. Proc. **36:** 2094–2099, 1977.

VALE, W., VAUGHAN, J., SMITH, M., YAMAMOTO, Y., RIVIER, J., AND RIVIER, C: Effect of synthetic ovine CRF, glucocorticoids, catecholamines, neurohypophysial peptides and other substances on cultured corticotropic cells. Endocrinology **113:** 1121–1131, 1983.

VALTIN, H.: Physiological effects of vasopressin on the kidney. *In* Vasopressin, ed. by D. M. Gash and G. J. Boer, pp. 367–387, Plenum Press, New York, 1987.

VANDENHEEDE, J. R., KAPPENS, S., AND DE WULF, H.: Inactivation and reactivation of liver phosphorylase b kinase. Biochim. Biphys. Acta **481:** 463–470, 1977.

VANDERWEL, M., LUN, D. S., AND HASLAM, R. J.: Vasopressin inhibits the adenylate cyclase of human platelet particulate fraction through V_1-receptors. FEBS Lett. **164:** 340–343, 1983.

VAN DE WERVE, G., HUE, L., AND HERS, H.-G.: Hormonal and ionic control of the glycogenolytic cascade in rat liver. Biochem. J. **162:** 135–142, 1977.

VAN LEEUWEN, F. W., VAN DER BEEK, E. M., VAN HEERIKHUIZE, J. J., WOLTERS, P., VAN DER MEULEN, G., AND WAN, Y.-P.: Quantitative light electron-microscopic autoradiographic localization of binding sites labelled with [^{3}H] vasopressin antagonist [d(CH_2)$_5$Tyr(Me)] AVP in the rat brain, pituitary and kidney. Neurosci. Lett. **80:** 121–126, 1987.

VAN LEEUWEN, F. W., AND WOLTERS, P.: Light microscopic autoradiographic localization of [^{3}H]arginine vasopressin binding sites in the rat brain and kidney. Neurosci. Lett. **41:** 61–66, 1983.

VAVRA, I., MACHOVÁ, A., HOLACEK, V., CORT, J. H., ZAORAL, M., AND SORM, J.: Effect of synthetic analogue of vasopressin in animals and in patients with diabetes insipidus. Lancet **1:** 948–952, 1968.

VAVREK, R. J., FERGER, M. F., ALLEN, G. A., RICH, D. H., BLOMQUIST, A. T., AND DU VIGNEAUD, V.: Synthesis of three oxytocin analogs related to [1-deaminopenicillamine]-oxytocin possessing antioxytocic activity. J. Med. Chem. **15:** 123–126, 1972.

VILHARDT, H., AND LUNDIN, S.: Antidiuretic antagonism and agonism of 1-deamino-pentamethylene-2-D-phenylalanine-4-isoleucine-arginine vasopressin in rats with diabetes insipidus. J. Endocrinol. **112:** 439–442, 1987.

VITTET, D., BERTA, P., MATHIEU, M. N., RONDOT, A., TRAVO, P., CANTAU, B., AND CHEVILLARD, C.: V_{1a} vasopressin-induced accumulation of inositol triphosphate in cultured rat aortic myocytes: modulation by protein kinase. Biochem. Biophys. Res. Commun. **140:** 1093–1100, 1986a.

VITTET, D., RONDOT, A., CANTAU, B., LAUNAY, J. M., AND CHEVILLARD, C.: Nature and properties of human platelet vasopressin receptors. Biochem. J. **233:** 631–636, 1986b.

VON CYON, E.: Die physiologischen Herzgifte. II. Hypophysenextracte. Pflugers Arch. **73:** 339–373, 1898.

VON DEN VELDEN, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen. Berl. Klin. Wochenschr. **50:** 2083–2086, 1913.

VORHERR, H., MASSRY, S. G., UTIGER, R. D., AND KLEEMAN, C. R.: Antidiuretic principle in malignant tumor extracts from patients with inappropriate ADH syndrome. J. Clin. Endocrinol. Metab. **28:** 162–168, 1968.

WAEBER, B., NUSSBERGER, B., HOFBAUER, K. G., NICOD, P., AND BRUNNER, H. R.: Clinical studies with a vascular vasopressin antagonist. J. Cardiovasc. Pharmacol. **8** (suppl. 7)**:** S111–S116, 1986.

WAEBER, B., SCHALLER, M. D., NUSSBERGER, J., BUSSIEN, J. P., HOFBAUER, K. G., AND BRUNNER, H. R.: Skin blood flow reduction induced by cigarette smoking: role of vasopressin. Am. J. Physiol. **247:** H895–H901, 1984.

WALKER, B. R.: Evidence for a vasodilatatory effect of vasopressin in the conscious rat. Am. J. Physiol. **251:** H34–H39, 1986.

WALKER, L. H., BUSCEMI-BERGIN, M., AND GELLAI, M.: Renal hemodynamics in conscious rats: effects of anesthesia, surgery, and recovery. Am. J. Physiol. **245:** F67–F74, 1983.

WEINAND, M. E., O'BOYNICK, P., AND OVERMAN, J.: Central antidiuretic hormone antagonism impedes development of vasogenic brain edema (abstr.). Presented at the Congress of Neurological Surgery, Baltimore, MD, in press, 1990.

WEITZMAN, R. E., REVICZKY, A., ODDIE, T. H., AND FISCHER, D. A.: Effect of osmolality of arginine vasopressin and renin release after hemorrhage. Am. J. Physiol. **238:** E62–E69, 1980.

WICKRAMASINGHE, S. N., VALDIMARSSON, H., AND WILLIAMS, B.: Interaction between a synthetic analogue of human vasopressin and human peripheral blood lymphocytes. J. Clin. Lab. Immunol. **7:** 67–70, 1982.

WILEY, M. K., PEARLMUTTER, A. F., AND MILLER, R. E.: Decreased adrenal sensitivity to ACTH in the vasopressin-deficient (Brattleboro) rat. Neuroendocrinology **14:** 257–270, 1974.

WOOD, J. M., STUDER, W., STOLDER, R., AND HOFBAUER, K. G.: Effects of endogenous arginine-vasopressin on renal, mesenteric and femoral vascular resistance in the rat. NZ Med. J. **96:** 918–920, 1983.

WOODS, R. L., AND JOHNSTON, C. I.: Contribution of vasopressin to the maintenance of blood pressure during dehydration. Am. J. Physiol. **245:** F615–F621, 1983.

WUTHRICH, R. P., AND VALLOTTON, M. B.: Prostaglandin E_2 and cyclic AMP response to vasopressin in renal medullary tubular cells. Am. J. Physiol. **251;** F499–F505, 1986.

WYSE, D. G.: In vitro arterial responses to vasopressin in subjects with a family history of hypertension. Hypertension **7:** 211–215, 1985.

YAMAMURA, H. J., GEE, K. W., BRINTON, R. E., DAVIS, T. P., HADLEY, M., AND WAMSLEY, J. K.: Light microscopic autoradiographic localization of [^{3}H]-arginine vasopressin binding sites in the rat brain. Life Sci. **32:** 1919–1924, 1983.

YAMANE, Y.: Plasma ADH levels in patients with chronic congestive heart failure. Jpn. Circ. J. **32:** 745–759, 1968.

YATES, F. E., RUSSELL, S. M., DALLMAN, M. F., HEDGE, G. A., MCCANN, S. M., AND DHARIWAL, A. P. S.: Potentiation by vasopressin of corticotropin-releasing factor. Endocrinology **88:** 3–14, 1974.

ZAORAL, M., KOLC, J., AND SORM, F.: Amino acids and peptides. LXXI. Synthesis of 1-deamino-8-D gamma-aminobutyrine-vasopressin, 1-deamino-8-D-lysine vasopressin and 1-deamino-8-D-arginine vasopressin. Coll. Czech. Chem. Commun. **32:** 1250–1257, 1967.

ZAORAL, M., AND SORM, F.: Synthesis of D-Dab^8-vasopressin. Coll. Czech. Chem. Commun. **31:** 310–312, 1966.

ZEGERS DE BEYL, D., NAEIJE, R., AND DE TROYER, A.: Demeclocycline treatment of water retention in congestive heart failure. Br. Med. J. **1:** 760, 1978.

ZERBE, R. L., BAYORH, M. A., AND FEUERSTEIN, G.: Vasopressin: an essential pressor factor for blood pressure recovery following hemorrhage. Peptides **3:** 509–514, 1982a.

ZERBE, R. L., FEUERSTEIN, G., MEYER, D. K., AND KOPIN, I. J.: Cardiovascular, sympathetic, and renin-angiotensin system responses to hemorrhage in vasopressin deficient rats. Endocrinology **111:** 608–613, 1982b.

ZERBE, R. L., STROPES, L., AND ROBERTSON, G. L.: Vasopressin function in the syndrome of inappropriate diuresis. Annu. Rev. Med. **31:** 315–327, 1980.

ZERBE, R. L., HENRY, D. P., AND ROBERTSON, G. L.: Vasopressin response to orthostatic hypertension. Am. J. Med. **74:** 265–271, 1983.

ZUSMAN, R. M., KEISER, H. L. AND HANDLER, J. S.: Effect of adrenal steroids on vasopressin-stimulated PGE synthesis and water flow. Am. J. Physiol. **234:** F532–F540, 1978.