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VASOPRESSIN V1a AND V1b RECEPTORS: FROM MOLECULES TO PHYSIOLOGICAL SYSTEMS

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Department of Pharmacology, Division of Molecular Pharmacology, Jichi Medical University, Tochigi, Japan; Department of Pharmacology, National Research Institute for Child Health and Development, Tokyo, Japan; Department of Pharmacy, Kyushu University Hospital, Fukuoka, Japan; and Department of Internal Medicine, Kitasato University, Kitasato Institute Medical Center Hospital, Saitama, Japan

Koshimizu T, Nakamura K, Egashira N, Hiroyama M, Nonoguchi H, Tanoue A. Vasopressin V1a and V1b Receptors: From Molecules to Physiological Systems. *Physiol Rev* 92: 1813–1864, 2012; doi:10.1152/physrev.00035.2011.—The neurohypophysial hormone arginine vasopressin (AVP) is essential for a wide range of physiological functions, including water reabsorption, cardiovascular homeostasis, hormone secretion, and social behavior. These and other actions of AVP are mediated by at least three distinct receptor subtypes: V1a, V1b, and V2. Although the antidiuretic action of AVP and V2 receptor in renal distal tubules and collecting ducts is relatively well understood, recent years have seen an increasing understanding of the physiological roles of V1a and V1b receptors. The V1a receptor is originally found in the vascular smooth muscle and the V1b receptor in the anterior pituitary. Deletion of V1a or V1b receptor genes in mice revealed that the contributions of these receptors extend far beyond cardiovascular or hormone-secreting functions. Together with extensively developed pharmacological tools, genetically altered rodent models have advanced the understanding of a variety of AVP systems. Our report reviews the findings in this important field by covering a wide range of research, from the molecular physiology of V1a and V1b receptors to studies on whole animals, including gene knockout/knockdown studies.

I. INTRODUCTION

The neurohypophysial hormone arginine vasopressin (AVP), which is also known as an antidiuretic hormone, is involved in a wide range of physiological regulatory processes, including renal water reabsorption, cardiovascular homeostasis, hormone secretion from the anterior pituitary, and modulation of social behavior and emotional status (292). AVP and the structurally related posterior pituitary hormone oxytocin (OT) are synthesized in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus (32) **(FIGURE 1)**. AVP and OT are also produced in other central areas and peripheral tissues (149, 178, 292). Axons of hypothalamic magnocellular AVP and OT neurons project to the neural lobe of the pituitary (32). Various signals from peripheral organs stimulate the release of AVP and OT. Either an increase in extracellular fluid osmolarity or a decrease in blood pressure (BP) stimulate the release of both AVP and OT, and lactation, labor, and nausea promote OT secretion. The parvocellular AVP and OT neurons in the PVN, on the other hand, project their neuronal axes to the portal capillary plexus of the external layer of the median eminence and induce the secretion of anterior pituitary hormones, such as adrenocorticotropic hormone (ACTH) (32). Parts of the parvocellular AVP and OT neurons project to other brain regions and also to spinal cords (441). In all vertebrate species studied to date, magnocellular and parvocellular AVP-like neurons are recognized in the preoptic area and anterior hypothalamus (179). AVP and OT are produced from larger precursor proteins, prepro-AVP and prepro-OT, respectively (4, 286). Prepro-AVP is cleaved in the secretory granules to produce a signal peptide of 19 amino acids, a nonapeptide AVP, neurophysin 2, and copeptin, whereas prepro-OT is processed to OT and neurophysin 1 (73, 92). Neurophysins work as carrier proteins for AVP and OT, whereas copeptin is a glycoprotein with no defined functionality.

Target organs and cells perceive hormonal stimuli mediated by AVP or OT through three distinct AVP receptors, V1a, V1b, and V2, and one OT receptor, all of which belong to a family of heptahelical guanine nucleotide-binding protein-coupled receptors (GPCRs) (51, 178, 495). The actions of AVP/OT through these receptors have been confirmed in

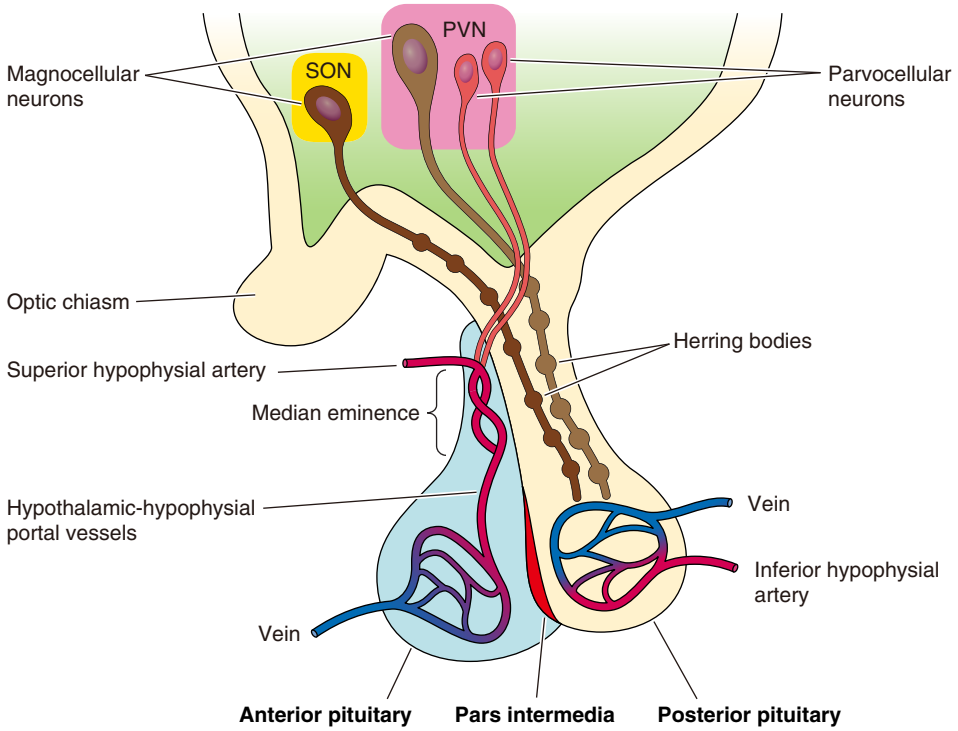


FIGURE 1. AVP neurons and the hypothalamo-pituitary system. Axons from magnocellular neurons in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus terminate in the posterior pituitary, which receives blood supply from the inferior hypophysial artery forming "the hypothalamo-neurohypophysial system." AVP is synthesized as prepro-AVP in the body of the neuron and passed down through the nerve axons. During the transfer, the precursor molecule is processed into AVP. AVP is then accumulated in the nerve terminals in the posterior pituitary and the Herring bodies (292). Parvocellular AVP neurons in the PVN, on the other hand, project their neuronal axes to the portal capillary plexus of the external layer of the median eminence. The hypothalamo-neurohypophysial portal vessels transfer released AVP from the median eminence to the anterior pituitary, where AVP stimulates ACTH release from corticotrophs.

many cell types. For example, the V1a (or V1) receptor is expressed in a variety of vascular walls in arteries, arterioles, and veins and is responsible for the vasoconstriction induced by AVP administration (348, 454). The V2 receptor is found in the renal distal tubules and collecting ducts, and stimulates water absorption (52, 312). The V1b (or V3) receptor in the anterior pituitary mediates the secretion of ACTH (471), and the OT receptor mediates uterine contraction and milk ejection (270). Far beyond these originally characterized functions of AVP and OT, a wealth of knowledge on the diverse roles of these hormones in the peripheral and central nervous system (CNS) has been accumulated. Herein, we summarize studies on AVP actions, which are correlated to the V1a and V1b receptors, using newly developed pharmacological and molecular tools and/or genetic animal models. We first review the molecular physiology of these receptors as a prototypical GPCR. The subsequent topics are subdivided into the peripheral and central roles of V1a and V1b receptors. The potential implications of the accumulated knowledge from basic research to the therapeutic use of receptor agonists and antagonists are discussed. Although AVP receptors are widely distributed throughout the whole body, combinations of newly developed pharmacological tools and genetically modified mouse models are useful to delineate the extent of direct AVP actions on the receptors.

II. STRUCTURE AND SIGNAL TRANSDUCTION

The molecular bases of the ligand-receptor interactions and signal transduction have been extensively studied using AVP/OT receptors. One advantage of studying AVP/OT receptors is the wide variety of peptide and non-peptide ligands developed so far, as well as detailed mutagenesis studies on receptor domains important for agonist and antagonist binding. Recent advances in the understanding of GPCR physiology indicate that receptor molecules interact with a number of other signaling molecules, as well as interacting with themselves. Every year, new studies reveal additional molecules with which receptor molecules interact. This trend requires an attempt to update and reconcile our knowledge of the actions of neurohypophysial hormones. In this section, we summarize the molecular bases for ligand-receptor interactions and protein-protein interactions involving V1a and V1b receptors.

Discoveries of the vasopressor effect and antidiuretic properties attributable to posterior pituitary extract led to clarification of the responsible ligands and their specific receptors in the target organs (227, 290, 385). The nonapeptide hormone AVP is structurally different from the related hormone OT at two amino acids (positions 3 and 8), and both peptides activate specific receptors that cause changes in several intracellular messengers, such as cAMP, Ca^{2+}, inositol 1,4,5-trisphosphate, and diacylglycerol, depending on the cell types examined (495). Molecular cloning of the three distinct AVP receptor subtypes, V1a, V1b, and V2, and the one OT receptor revealed a well-conserved ligand-receptor system in humans, rodents, and other mammals as well as in nonmammal species (179, 495). Comparing the functional similarity and diversity of the AVP/OT receptors has significantly advanced our understanding of the mechanisms of ligand perception and subsequent intracellular events (40, 496). V1a, V1b, and OT receptors effectively couple to the G_q and phospholipase C (PLC) pathway, and the V2 receptor couples to the G_s and adenylate cyclase pathway (40, 178, 225, 496). Amino acid identities among a family of AVP/OT receptors are 42–55% in humans. Furthermore, these isoforms are highly conserved from one species to another, the homology being up to 90% for a given subtype (292). In addition, one of the distinguishing characteristics of AVP-like and OT-like receptor genes from all species is consistent interruption of the coding sequences between transmembrane domains 6 and 7 by a conserved intron (357). These highly conserved structures in both ligands and receptors make the AVP/OT receptor family an excellent model system to study GPCR functions in detail. Thus efforts have been made to localize amino acid(s) or domains in the V1a and V1b receptors responsible for their particular functions in studies that compared them with each other or with V2 or OT receptors. In this section, we review the current knowledge obtained mainly from in vitro studies on the biochemical and molecular biological bases of V1a and V1b receptor physiology. Specifically, ligand-receptor interactions and interactions between a receptor and other signaling molecules are discussed. The bibliography dealing with V1a and V1b receptors includes several hundred publications. Because of space limitations, we cannot cite a large number of original works, but previous reviews will provide a basis for exploring the details of such studies (51, 224, 483, 495, 496, 522).

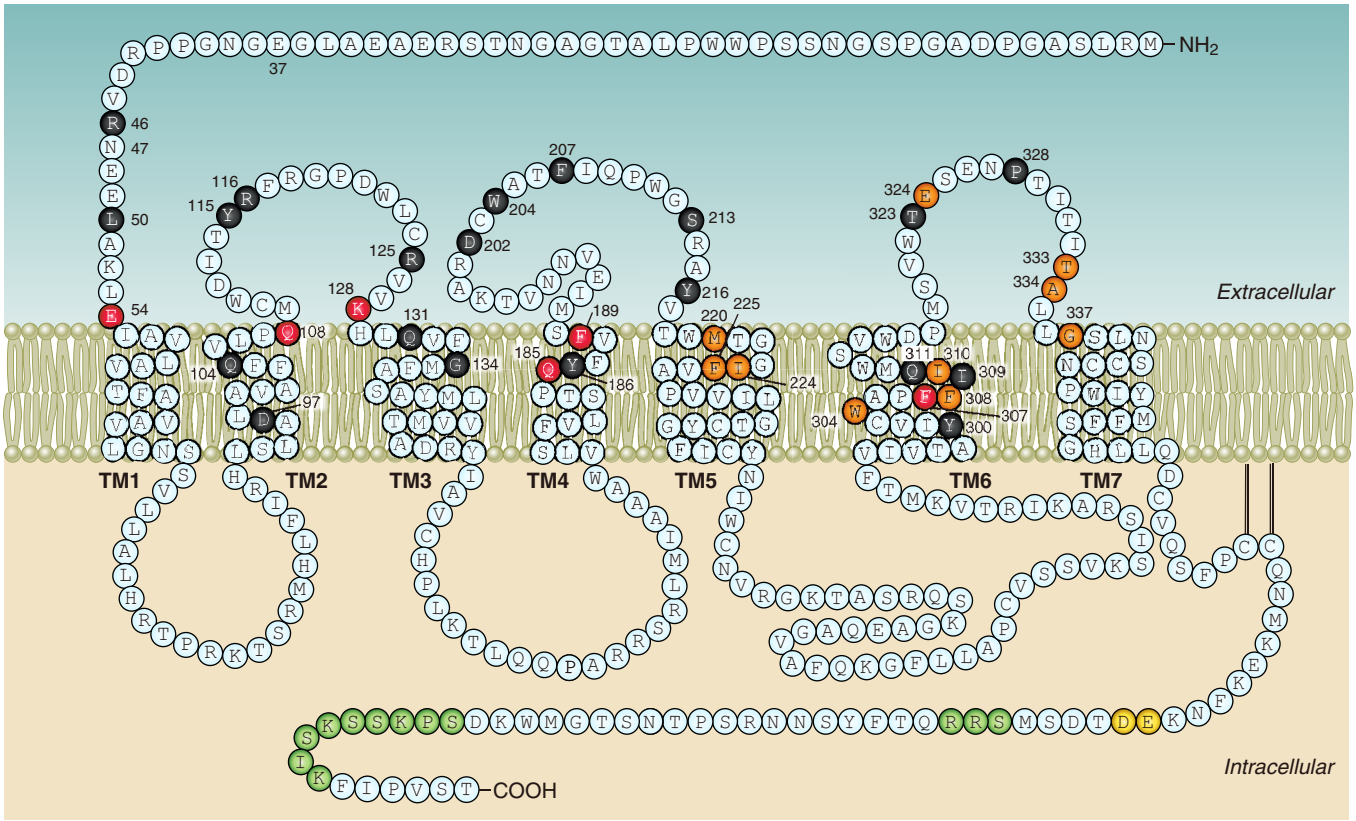
A. Ligand Binding and Selectivity

Recent progress and successes in determining the structures of GPCRs have yielded valuable information on the binding mode of nonpeptide and peptide ligands (276, 394, 413). Although the structures of AVP and OT receptors have not yet been conclusively determined, previous physiological and modeling studies have identified key amino acid residues for agonist and antagonist binding to V1a and V1b receptors (323, 453, 495).

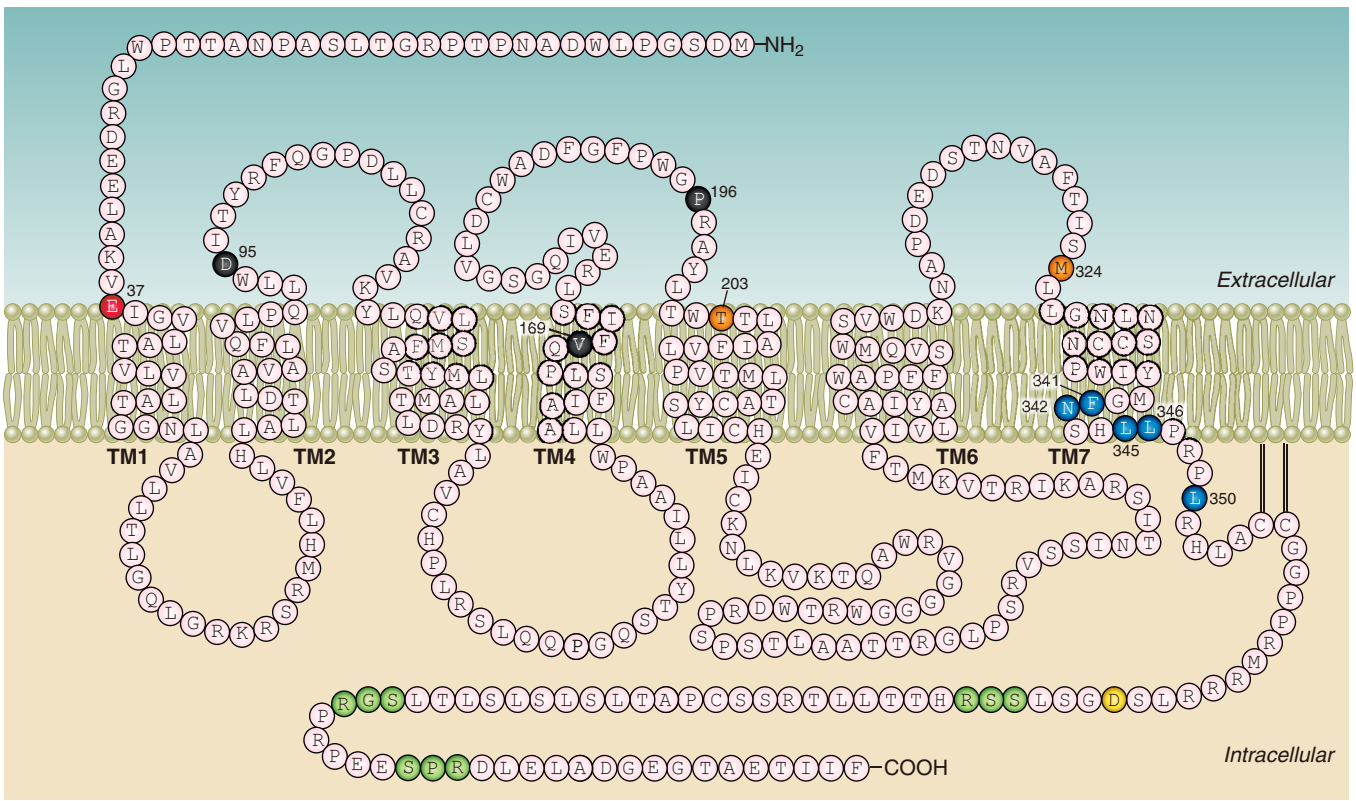
In an early mutagenesis study on the V1a receptor, the effect of changing each polar glutamine residue in transmembrane (TM) 2, 3, 4, and 6, or lysine in TM3 of the rat V1a receptor to alanine significantly reduced the binding affinities of agonists, but resulted in only minor changes in the binding affinities of antagonists. This indicates a different binding mechanism for agonists and antagonists toward the V1a receptor. The critical amino acids, Q104A, Q108A, Q131A, Q185A, Q311A, and K128A, are depicted in **FIGURE 2*A*** (354, 355). The binding affinities of OT to the mutant V1a receptors were more profoundly affected than those of AVP (354, 355) **(FIGURE 2*A*)**. On the other hand, a short subdomain located in the amino (NH_2)-terminus of the rat V1a receptor from Glu-37 (E37) to Asn-47 (N47) is an absolute requirement for the binding of AVP and other agonists, but deleting this segment has little or no effect on the binding of either peptide or nonpeptide antagonists. Transfer of the corresponding NH_2-terminal segment of the OT receptor to the V1a receptor generated a chimeric OT-V1a receptor, which possessed pharmacological and signaling profiles similar to wild-type (WT) V1a receptors (208). Thus the E37-N47 segment in the NH_2 terminus of the V1a receptor and the corresponding segment of the OT receptor are required for AVP binding, but are not responsible for agonist selectivity. Subsequently, a single residue, Arg-46 (R46), within the E37-N47 segment of the NH_2 terminus of the rat V1a receptor, was shown to be critical for the binding of the receptor agonists, but not antagonists, and for the transduction of the intracellular signal. Similarly to R46, Glu-54 (E54) is also critical for the binding of V1a receptor agonists. R46, which is located just outside TM1, and E54 in TM1 near R46, are conserved in other members of mammalian AVP/OT receptor families and also in other vertebrate and invertebrate nonapeptide receptor families, such as the vasotocin (AVT) receptor for invertebrates, and isotocin and mesotocin receptors for fish and birds (204, 209, 210).

The role of charged residues in extracellular loops, which are conserved in a subfamily of peptide-GPCRs, were examined systematically using mutagenesis and the modeling method on the rat V1a receptor (207). Arg-116 (R116; in the first extracellular loop, ECL1), Arg-125 (R125; at the top of TM3), and Asp-204 (D204; in ECL2 of rat V1a receptor) are important for agonist binding and/or receptor activation. Asp-204 (D204) corresponds to Asp-202 (D202) in the human V1a receptor **(FIGURE 2*A*)**. Further analysis of ECL2 by alanine-substitution mutagenesis revealed that four conserved aromatic residues among the receptors for hypophysial nonapeptides, Phe-189 (F189), Trp-206 (W206), Phe-209 (F209), and Tyr-218 (Y218) in the rat V1a receptor, which correspond to Phe-189 (F189), Trp-204 (W204), Phe-207 (F207), and Tyr-216 (Y216) in the human V1a receptor, are necessary for ligand binding and receptor activation (96, 207). By comparing interspecies differences between the rat V1a and amphibian V1-type vasotocin receptor

A Human V1a receptor



B Human V1b receptor



(VT1), the binding affinities of AVP or AVT to the receptors were examined (3). The V1a receptor responded better to AVP than AVT, whereas the VT1 receptor exhibited higher sensitivity to AVT than AVP. The triple mutations F313Y/I315T/P334T of the rat V1a receptor, which correspond to Phe-307 (F307), Ile-309 (I309), and Pro-328 (P328) in the TM6 of the human V1a receptor, or a double mutation Y306F/T327P, which correspond to Tyr-300 (Y300) and Thr-323 (T323) in the TM6 of the human V1a receptor, effectively exchanged mutual binding characters (3). These studies identified the structural requirements of the V1a receptor for high-affinity agonist binding and conformational activation.

Both native ligands, AVP and OT, can bind to AVP and OT receptors with different affinities (178, 495). Representative tissues and cloned receptors expressed in a cell line were used to characterize ligand selectivity of each receptor subtype. Liver and vascular tissues were used for the analysis of V1a receptors, pituitary and pituitary tumors for V1b receptors, kidney for V2 receptors, and uterus and mammary gland for OT receptors. Radioligand binding studies using tritium-labeled AVP ([^{3}H]AVP) or OT ([^{3}H]OT) demonstrate that AVP binds to all three AVP receptors and also to the OT receptor in a relatively nonselective manner **(TABLE 1)**. In fact, a <10-fold difference was noted between the K_i values of AVP binding to the V1a receptor and to the OT receptor, when these receptors were individually expressed in a cell line and examined in radioligand binding experiments (90, 269, 311, 495). On the other hand, OT binds to the OT receptor with significantly higher affinity than AVP receptors. The K_i values for OT binding to the OT receptor are 10–100 times smaller than those for OT binding to the V1a receptor (90, 208, 495). How OT differentially binds to V1a and OT receptors was examined in the V1a receptor mutants and in a three-dimensional modeling study, which revealed that Tyr-115 (Y115) of the rat V1a receptor in the ECL1 may interact with Arg-8 of AVP (90). Substitution of this Y115 to leucine (Y115L) significantly impaired the binding of AVP to the mutant receptor. When the Y115 of the V1a receptor was replaced with the corresponding phenylalanine of the OT receptor (Y115F) or aspartic acid of the V2 receptor (Y115D), the binding affinities of the mutant V1a receptor toward OT or V2-selective agonists were increased. Thus Y115 in the ECL1 is critical for the high-affinity binding of agonists and for ligand selectivity (89, 90). The other amino acids important for the binding of AVP to the V1a receptor include Leu-50 (L50) (210), Asp-97 (D97) (354), and Gly-134 (G134) (494).

Table 1. *Affinity of vasopressin and structural analogs for the human V1a, V2, and V1b receptors and OT receptor stably expressed in CHO cells*

	K_i, nM			
	hV1a	hV2	hV1b	hOT
AVP	1.7 ± 0.08	1.1 ± 0.1	1.1 ± 0.05	1.65 ± 0.49
Oxytocin	64 ± 12	167 ± 12	1,782 ± 79	0.79 ± 0.22
AVT	5.0 ± 0.3	6.2 ± 0.1	10 ± 1.1	0.36 ± 0.10

Data are from Chini et al. (90) and Thibonnier et al. (497).

In addition to endogenous ligands, represented by AVP and OT, significant efforts have been made to develop a number of synthetic agonists and antagonists with a variety of subtype specificities. Because of space limitations and the existence of several excellent reviews (88, 194, 323), the focus of this review is on the biochemical bases of these subtype-selective ligand binding properties, obtained from molecular biological and modeling studies of V1a and V1b receptors.

A nonpeptide V1a receptor antagonist OPC-21268 was revealed to have a high affinity for the rat V1a receptor, but a lower affinity for the human V1a receptor (494, 499). The single or double amino acid substitutions of the human V1a receptor at I224V, I310V, G337A, G337A/I310V, G337A/E324D, or G337A/I224V to the corresponding rat V1a receptor sequence dramatically increased the affinity of the rat V1a receptor antagonist OPC-21268, whereas the binding of AVP, as well as that of a peptide V1a receptor antagonist d(CH_2)$_5$[Tyr(Me)^2]AVP (which later turned out to be a mixed V1a/OT receptor antagonist), and a selective nonpeptide V1a receptor antagonist SR49059, were minimally altered (494). Binding sites of SR49059 to the human V1a receptor, on the other hand, were analyzed using a site-directed irreversible labeling strategy that combines mutagenesis of the receptor and binding of chemically reactive probes derived from SR49059 (480). This generates a chemical bond between the cysteine residue incorporated into the receptor and the sulfhydryl-reactive group in the SR49059 analog. Combined with three-dimensional modeling of the receptor, this approach revealed that Phe-225

FIGURE 2. Amino acid residues important for ligand binding to human V1a and V1b receptors. Amino acids important for agonist binding, antagonist binding, and both agonist and antagonist binding to V1a (*A*) and V1b (*B*) receptors are colored black, orange, and red, respectively. In the diagram of the V1b receptor (*B*), amino acids important for the exit of the receptor from the endoplasmic reticulum are blue. Transmembrane (TM) topology is from Thibonnier et al. (494). In the COOH terminus, GRK consensus motifs of diacidic or acidic amino acids upstream of serine residues are yellow, and PKC consensus motifs (S/T)X(R/K) are green. Findings obtained from species other than human are translated to the corresponding amino acids of the human V1a or V1b receptors. Palmitoylated cysteines in the COOH terminus are connected to the plasma membrane. [From Thibonnier et al. (494), with permission from American Society for Pharmacology and Experimental Therapeutics.]

(F225) in the TM5 directly participates in the binding of the V1a receptor antagonist SR49059 (480). In the TM6, the mutation of three aromatic residues of the human V1a receptor, Trp-304 (W304), Phe-307 (F307), and Phe-308 (F308), reduced affinity for $d(CH_2)_5[Tyr(Me)^2]AVP$ and SR49059, but not for AVP binding, suggesting that these amino acids are necessary for agonist/antagonist discrimination (99). The hydrophilic residues Gln-108 (Q108), Lys-128 (K128), and Gln-185 (Q185) in the TM2, TM3, and TM4 of the human V1a receptor, respectively, are needed for high-affinity binding of both agonists and antagonists. The residues Thr-333 (T333) and Ala-334 (A334) in the ECL3 near the TM7 control the binding selectivity of the V1a/V2 receptors for both nonpeptide and cyclic peptide antagonists (99).

Although the interaction between the V1a receptor and its ligands has been well characterized, relatively few studies have been published on the V1b receptor structure. The characteristics of V1b receptor-specific binding have also been the subject of mutagenesis experiments **(FIGURE 2*B*)**. When two conserved residues, Glu-37 (E37) and Asp-95 (D95), which are located in the TM1 and just outside the TM2 of the human V1b receptor, respectively, were mutated by alanine, E37A, and D95A, each single amino acid substitution significantly affected the binding affinity of [^{3}H]AVP to the V1b receptor mutants (426). Moreover, the binding affinities of the two peptide V1b receptor agonists tested (d[Cha^4]AVP and dDAVP) were significantly decreased in the E37A V1b receptor mutant (by at least 135-fold). AVP-derived peptide d[Cha^4]AVP exhibited a much stronger affinity for the human V1b receptor than for the human V1a receptor subtype. The V1a receptor mutant bearing two V1b residues at Y186V in the TM4 and at S213P just outside the TM5 resulted in an increased affinity for d[Cha^4]AVP, suggesting that these two residues are important for V1b receptor-like binding properties (426). Binding properties of the selective peptide V1a receptor agonist F-180 or the V1a receptor antagonist SR49059 to this double mutant receptor were almost unchanged. On the other hand, the mutation of E37A in the V1b receptor resulted in a dramatically decreased affinity for the nonpeptide V1b receptor antagonist SSR149415 (K_i >10,000 nM) (426, 452). Thus E37 in the V1b receptor is necessary for the subtype-specific binding of both agonist d[Cha^4]AVP and antagonist SSR149415. Mutant V1a receptors with V1b receptor-derived amino acids at position 220 (M220T) or 334 (A334M) exhibited a striking increase in affinity for SSR149415 and retained relatively high affinity for the peptide agonist F-180 and nonpeptide antagonist SR49059 specific to the V1a receptor (118). Therefore, although V1a and V1b receptors preserve high amino acid similarity, the amino acid positions responsible for V1b receptor-like selectivity are different from those for V1a receptor-like binding properties.

As a result of significant efforts to enhance our understanding of AVP and OT binding to V1a and V1b receptors, it is becoming clear that the extracellular and TM domains contribute to ligand-receptor interactions to various extents. Although the whole picture of agonist-induced receptor activation remains to be clarified, information from these studies is valuable for further modeling and structural investigations.

B. Protein-Protein Interactions and Signal Transduction

Activated V1a and V1b receptors interact with the G_q subtype heterotrimeric G protein and enhance the exchange of guanine nucleotides from GDP to GTP (251, 495). In addition to this G protein-dependent signaling, the G protein-independent β-arrestin-dependent signaling pathway is also activated by AVP (410, 417, 491). Thus receptors for AVP/OT have been well characterized as prototypical GPCRs. In this section on signal transduction, we mainly focus on the findings related to V1a and V1b receptors, but studies on V2 and OT receptors that helped advance our understanding of the V1a and V1b receptors are also introduced.

Upon stimulation by AVP, the V1a receptor is rapidly phosphorylated and desensitized (235). Receptor phosphorylation generally occurs in two ways: agonist-dependent phosphorylation by G protein-coupled receptor kinases (GRKs) and phosphorylation by intracellular messenger-dependent kinases, such as protein kinase C (PKC) (150). The human V1a receptor physically associates with PKC-α under basal conditions (46). After agonist stimulation, PKC-α dissociates from the V1a receptor. The V2 receptor, on the other hand, does not associate with PKC-α either before or after the stimulation. The V1b and OT receptors associate with PKC-α only after receptor stimulation (46). Examination of the amino acid sequences of human AVP/OT receptors reveals that the carboxy (COOH) terminus of the V1a receptor contains one proximal GRK consensus motif (a diacidic motif upstream of serine residues) and three distal PKC consensus motifs [(S/T)X(R/K)], whereas the COOH terminus of the V2 receptor contains one GRK consensus motif but no PKC consensus motif. The COOH terminus of the V1b receptor contains one GRK and two PKC consensus motifs **(FIGURE 2)**. Finally, the COOH terminus of the OT receptor contains three PKC, but no GRK, consensus motifs (46, 498). In studies on human AVP/OT receptors, the COOH termini of V1a and V2 receptors specifically associated with GRK5 and/or PKC-α in a receptor subtype-specific manner modulated by agonist stimulation. Deletion, substitution, and point mutation of the kinase consensus profoundly impacted the receptor-kinase interactions (46). After AVP stimulation, GRK5 briefly associated with the V1a and V1b receptors after 0.5 min of stimulation and also with the V2 receptor after 5 min. No association of GRK with the OT receptor was detected. The time course

and mode of receptor phosphorylation were reversed by exchanging the receptor COOH termini of the V1a and V2 receptors. Therefore, receptor subtype-specific interactions with GRK and PKC are dependent on the COOH-terminal structures (46). In HEK cells, phosphate incorporation into the V1a receptor reaches its maximum after 15 s; after removal of AVP, it decays with a half-life of 6 min (234). The V2 receptor, on the other hand, is phosphorylated at a slower rate than the V1a receptor, and phosphate is retained for a longer period in both the presence and absence of the agonist (233).

Corresponding to the dephosphorylation kinetics, internalized V1a receptors rapidly returned to the cellular surface, but internalized V2 receptors associated with β-arrestin remained intracellular for a longer period in the perinuclear recycling compartment, which contains the small GTP-binding protein Rab11 (233, 381). The rapid internalization and recovery of the V1a receptors expressed in HEK cells corresponded well to the internalization kinetics of hepatic V1a receptors (156). Internalization of hepatic AVP binding sites occurs with a half-life of 3–6 min; after removal of the agonist, the cell surface binding sites rapidly returned with a half-life of 8–10 min at 18°C (156). Receptor internalization was dependent on β-arrestin, as confirmed by coexpression of a dominant negative arrestin (the last 100 amino acids of arrestin), which reduced the internalization of V1a and V2 receptors (64). Although coexpression of the V1a receptor with β-arrestin 2, but not with β-arrestin 1, promoted the receptor internalization, both arrestins promoted V2 receptor internalization (64). A single mutation, S363A in the COOH terminus of the V2 receptor, accelerated the dephosphorylation of the protein and conferred recycling properties to the V2 receptor, indicating that dephosphorylation is required for the receptor to return to the cell surface (64, 234, 236). Because this rapidly recycling S363A mutant receptor interacted with β-arrestin and targeted the perinuclear recycling compartment, as seen in the wild-type V2 receptor, the interaction between the receptor and β-arrestin is not considered to be a requirement for the intracellular retention of the V2 receptor (233).

In addition to these agonist-dependent changes in intracellular receptor localization, analysis of plasma membrane sorting of the human V1b receptor identified a novel endoplasmic reticulum (ER) export signal corresponding to the hydrophobic region of the proximal COOH terminus. This signal consists of an $FN(X)_2LL(X)_3L$ motif, as shown in **FIGURE 2*B***. Its disruption impaired ER export and transport of the receptor to the cell surface (423). Moreover, the V1b receptor antagonist SSR149415 rerouted the mutated receptor to the plasma membrane (422). Thus SSR149415 worked as a novel pharmacological chaperone for the V1b receptor. A similar pharmacological chaperone has been identified for mutant V2 receptors responsible for nephrogenic diabetes insipidus (DI) caused by the inability of the mutant receptors to reach the cell surface membrane (351). The pharmacological chaperones are low-molecular-weight compounds, which enter cells, bind specifically to misfolded mutant proteins, correct their folding, and allow them to escape from the intracellular compartment (95). Interestingly, the $FN(X)_2LL(X)_3L$ motif of the V1b receptor is located in the "fourth intracellular loop" between the TM7 and putative palmitoylated cysteines (see **FIGURE 2*B***). In the human V2 receptor, a dileucine sequence with an upstream glutamate residue, ELRSLLCC, where the double cysteines are putative palmitoylation sites, is critical for the escape of the receptor from the ER (446). The disease-causing nonsense mutation R337X within the retention motif causes the truncated mutant V2 receptor to display an extended interaction with calnexin and ER retention (95, 352). Because calnexin also colocalized with the mutant V1b receptor at the $FN(X)_2LL(X)_3L$ motif, calnexin may work as a molecular chaperone for the quality control and ER retention of misfolded GPCRs (95, 352, 422).

In addition to protein-protein interactions between receptor and signaling molecules, functional diversities of GPCR-mediated signaling events are extended by receptor dimerization and even higher orders of oligomerization (63, 341, 431, 492). Two of the same receptor units can form a homomeric dimer, whereas two different receptor monomers can form a heteromeric dimer receptor with novel physiological properties (63). This also applies to the cloned AVP and OT receptors when heterologously expressed in cell lines (88, 100, 120, 121, 490, 493). Coimmunoprecipitation experiments detected receptor homodimers of the V1a, V2, and OT receptors, as well as heterodimers composed of all possible combinations of two of these three receptors (493). AVP/OT receptor dimers are reportedly stable against stimulation and formed together with synthesis of receptor polypeptides (15, 490–493). When these receptors were tagged at COOH termini either with a *Renilla* luciferase (Rluc), or yellow fluorescent protein (YFP), and differently tagged receptor fusion proteins were coexpressed in HEK cells, bioluminescence resonance energy transfer (BRET) was detected between the Rluc- and YFP-fusion constructs. Concerning heterodimers formed between the AVP receptor and other receptor family members, the V1b receptor was reported to form a heterodimer with the CRHR1 receptor (358, 545). On the other hand, none of the V1a, V2, or OT receptors formed efficient heteromers with the $GABA_{(B2)}$ receptor subunit (493).

The functional consequence of dimerization between V1a and V2 receptors was examined in terms of the intracellular localization of the receptors. As mentioned above, the internalization and recycling time course of V1a and V2 receptors is markedly different (233). β-Arrestin dissociates rapidly from the V1a receptor, allowing its rapid recycling to the plasma membrane, but β-arrestin remains associated

with the V2 receptor in the endosomes, leading to intracellular accumulation of the V2 receptor. In cells coexpressing V1a and V2 receptors, nonselective agonist stimulation made the heterodimer receptor stably internalized and localized with β-arrestin. Therefore, the rapid recycling character of the V1a receptor was altered in the V1a/V2 heteromer (490). The V2 receptor mutant with R137H, which is constitutively internalized and colocalized with β-arrestin, also made the coexpressed V1a receptor internalized without an agonist. When coexpressed cells were stimulated with the V1a receptor agonist F-180 (23), internalized V2 receptors were detected, and both receptors efficiently recycled to the plasma membrane. These results suggest that activation of only one protomer is sufficient to promote the internalization of the receptor complex and that recycling kinetics are dependent on the interaction between the receptor and β-arrestin (490).

Receptor heteromerization can alter the cooperativity of ligand binding (131, 158, 159, 461). This possibility was examined in CHO cells expressing V1a, V1b, and OT receptors (14, 388). Receptor-receptor interaction at the cell surface was examined by time-resolved fluorescence resonance energy transfer (TR-FRET), in which V1a and V1b receptors were tagged at the NH_2 terminus with HA or 6-His and recognized with antibodies labeled with the fluorescent probes europium cryptate-pyridine bipyridine or Alexa Fluor 647. The long lifetime of the emission fluorescence from europium cryptate allows a TR-FRET, avoiding any signal contamination generated by shorter-lived signals (14, 327, 388). Excitation of europium cryptate-pyridine bipyridine at 337 nm resulted in a TR-FRET signal measured at 665 nm (the emission wavelength of Alexa Fluor 647). This result indicates that differently tagged V1a receptor NH_2 termini are in close proximity, usually within the 1- to 10-nm range (253), and that V1a as well as V1b receptors result in homodimerization in the plasma membrane (14, 388). A saturation radioligand binding and homologous competition binding study using [^{3}H]AVP or [^{3}H]OT on membranes prepared from V1a, V1b, or OT receptor-expressing cells demonstrated negative cooperativity with n_H values from the Hill coefficient being less than 1 (14). The Hill equation is $B = B_{max}\ [1 + (K_d/[L])^{n_H}]^{-1}$, where B_{max} is the maximal binding, [L] is the concentration of the labeled ligand, K_d is the equilibrium dissociation constant for the labeled ligand, and n_H is the Hill coefficient (448). The negative cooperativity in [^{3}H]AVP binding to V1a receptors lacks sensitivity to the nonhydrolyzable GTP analog GTPγS (14). Thus the binding of a first ligand can modulate the binding of a second one to V1a, V1b, and OT receptors.

The TR-FRET method initially used to detect receptor-receptor interactions was further extended to examine receptor-ligand and even ligand-ligand interactions (15, 16, 100). To realize a more efficient energy transfer signal between receptors, the tag-lite strategy was employed (326). Chimeric receptor proteins were first designed by fusion with a SNAP-tag at the receptor NH_2 termini, and the tagged receptor in the cell surface was labeled with fluorescent substrates with high efficiency (326). The FRET signal between the fluorescent-labeled receptor and the fluorescent ligand can be evaluated as the affinity measurement. Because the size of the SNAP-tag is about one-eighth of an antibody, the distance between fluorophores can be reduced. One advantage of using the TR-FRET method is that a lowered background-homogeneous assay design with membrane preparation is also possible, allowing the development of a high-throughput screening protocol (15, 16, 100). For the detection of FRET between ligands, a variety of AVP-derived ligands were labeled with lanthanide cryptate (either europium pyridine-bis-bipyridine or Lumi4-Tb) as the donor fluorophore and Alexa Fluor 647 as the acceptor, and the TR-FRET signal was detected in transfected V1a, V2, and OT receptors (15). Labeled antagonists produced stronger FRET signals than did agonists, indicating that simultaneous receptor occupancy is more frequent in antagonist pairs. Furthermore, the specific TR-FRET signal between ligands can be used to demonstrate the asymmetric relationship of two oxytocin receptor protomers and receptor-receptor interactions in native tissues (15). However, whether or not the different AVP receptors and OT receptors heterodimerize in vivo is not known. It should be pointed out that rich sources of synthetic ligands and knowledge of ligand-receptor interactions allow the AVP/OT receptor system to act as a prototypical GPCR family member. This has helped to extend our understanding of receptor physiology.

III. V1a AND V1b IN PERIPHERAL TISSUES

V1a and V1b receptors are expressed in many peripheral tissues as noted above. Genetic studies on the correlations between variations of the V2 receptor gene and the resultant phenotypes in humans have improved our understanding of V2 receptor functions in vivo and in vitro. In contrast to V2 receptors, the functional importance of native V1a and V1b receptors was not clearly understood until studies using ligands with acceptable subtype selectivity or genetically modified animals were performed. Here, we summarize recent advances in knowledge that have resulted from studies using receptor-KO mice and corresponding studies using pharmacological tools.

A. Cardiovascular Function

A wide range of AVP functions in the cardiovascular system have been extensively investigated in normal and disease states. The complex roles of AVP in regulating circulatory function are mediated by the receptors in multiple cardio-

vascular and extracardiovascular tissues (256). Among the variety of AVP actions, it is certain that the antidiuretic properties mediated by V2 receptors are of physiological importance as they control renal water reabsorption through aquaporin (AQP) water channels (5, 374). In contrast, the contribution of V1a receptors to the BP homeostasis of normal subjects remains unclear, even though AVP administered from an external route can induce a large increase in BP. This is because the plasma AVP concentration is lower than that needed to activate the vasopressor response mediated by the V1a receptor (302, 346). It is, however, becoming clear that AVP receptors located outside the cardiovascular organs play a critical role in BP control. AVP is involved in cardiovascular homeostasis through regulating *1*) systemic BP and vascular tonus, *2*) baroreceptor reflex (baroreflex) and sympathetic nerve stimulation in the CNS, *3*) cardiac function, *4*) renal function, and *5*) interaction with other hormones **(FIGURE 3)**. In this section, we summarize the recent findings on cardiovascular physiology mainly related to V1a receptors derived from studies that employed genetically modified animal models and physiological techniques directed toward these receptors. A more historical and broader view of previous reviews can be found in various reports (110, 224, 256, 302, 365, 454).

1. Vasoconstriction and BP control

AVP and related peptides have been repeatedly demonstrated to be strong vasoconstrictors in many vascular beds (365, 454). In the regulation of systemic BP, vascular tonus and blood volume are precisely controlled by neural and hormonal regulator systems. Feedback signals from peripheral circulation on blood osmolarity and vascular tonus are integrated in the AVP neurons to regulate hormone secretion from the posterior pituitary (104). Among the AVP receptors, the actions of the renal V2 receptor are under strict control by the physiological range of plasma AVP concentrations (425). After overnight fasting, plasma AVP levels of normally hydrated human subjects are typically between 2 and 4 pg/ml and between 20 and 30 pg/ml under water restriction (101, 290). In isolated rat mesenteric arteries, such physiological concentration(s) of AVP can induce contractive responses at as low as 1 pM, which is roughly equivalent to 1.08 pg/ml if the molecular weight of AVP is calculated as 1084.3 (21), although substantial variety in the sensitivity to AVP depending on the vasculatures (21, 212). On the other hand, it has been noted that the blood AVP levels necessary for increasing the systemic BP are much higher than those for exerting the antidiuretic effect (302, 454). The threshold plasma AVP concentration needed to raise mean arterial pressure by more than 5 mmHg exceeded plasma AVP levels of 42 pg/ml, nearly twice that needed to achieve maximum antidiuretic activity (101). Moreover, AVP enhances the baroreflex control of heart rate (HR), in which an increase in BP can be attenuated by the reflex control of slowing the HR (102, 344). These observations led to the conclusion that BP changes due to an increase in a small dose of AVP may be obscured by enhanced baroreflex control (302). In fact, intravenous administration of the mixed V1a/OT receptor antagonist $d(CH_2)_5[Tyr(Me)^2]$AVP into well-hydrated and resting human subjects did not alter BP (80). These results, together with findings on the strong influence of autonomic and renin-angiotensin-aldosterone systems on cardiovascular control, indicate that the AVP and vascular V1a receptor systems play a relatively minor role in the regulation of BP. Under pathophysiological conditions, however, such as severe hypovolemia, hypotension, autonomic failure, general anesthesia, and hemorrhage, high AVP concentrations in the blood have been reported to play an important vasopressor role (67, 102, 257, 454, 509, 530).

To evaluate the functional role of the V1a receptor on regulating vascular tonus and BP, V1a receptor knockout (V1aR-KO) mice were investigated for cardiovascular phenotypes. The conventional gene knockout techniques inactivate a gene throughout the entire life of mice, which may cause some compensatory change in the genetically modified mice and obscure experimental findings. In the case of GPCR gene knockout mice, however, the effect of gene knockout might be confirmed by using receptor blockers, if available, on WT animals. In studies with isolated and perfused mesenteric arterial beds, the AVP-induced pressor response was lost in preparations from V1aR-KO mice, indicating that the V1a receptor is responsible for AVP-induced vascular contraction (278). Intravenous administration of AVP caused a prompt and potent pressor response in a dose-dependent manner in control WT mice, but not in V1aR-KO mice. In V1aR-KO mice, AVP caused a decrease in BP at relatively high concentrations. The AVP-induced decrease in BP observed in V1aR-KO mice was blocked by pretreatment with a selective V2 receptor antagonist, [adamantaneacetyl^1,*O*-ethyl-D-Tyr-2,Val-4,aminobutyryl^6,Arg-8,9]-vasopressin. Furthermore, pretreatment with an inhibitor of nitric oxide synthesis, N^{ω}-nitro-L-arginine, markedly shortened the duration of the AVP-induced BP decrease. These findings from studies with V1aR-KO mice confirmed the differential roles of V1a and V2 receptors in regulating vascular tonus by AVP (278). AVP-induced vasodilatation (presumably via the V2 receptors) has previously been reported in renal and central arteries and veins in various species, including dog (301), rat (524), and human (222, 473). In the pulmonary artery, on the other hand, AVP-induced vasodilatation is inhibited by a mixed V1a/OT receptor antagonist (145, 488).

Under waking and free-movement conditions, the diastolic and systolic BP of V1aR-KO mice was unexpectedly lower compared with that of control WT mice without a notable change in HR (278). This finding indicates that AVP/V1a receptor actions are necessary for maintaining the basal BP. However, the lack of vascular V1a receptors is not consid-

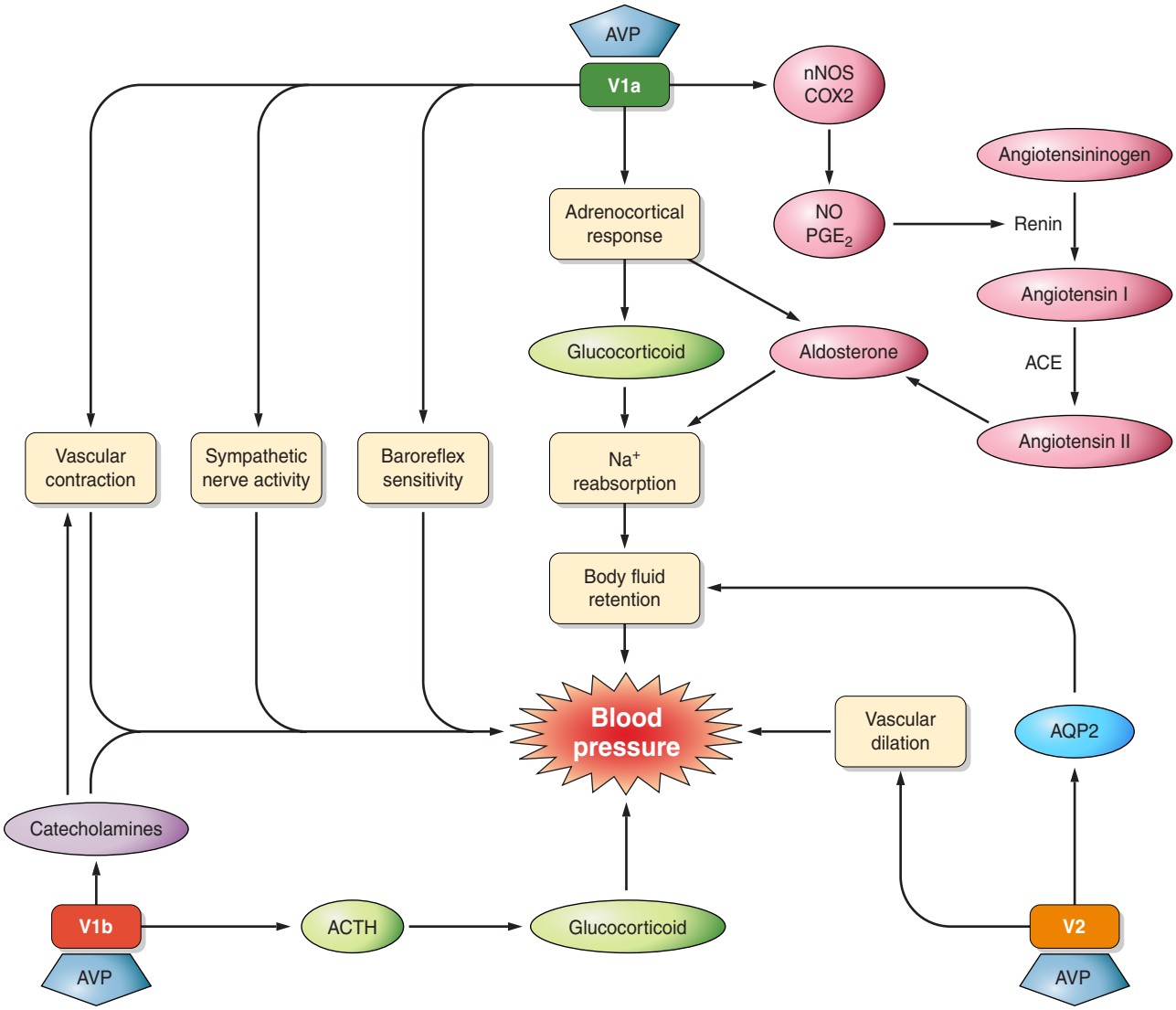


FIGURE 3. Contributions of AVP and its receptors to the regulation of BP homeostasis. AVP is involved in the regulation of BP homeostasis via V1a, V1b, and V2 receptors. AVP regulates vascular contraction, aldosterone/glucocorticoid release from the adrenal gland, renin production in the kidney, and sympathetic nerve activity and baroreflex in the CNS, through the V1a receptors. AVP also stimulates ACTH and catecholamine release from the anterior pituitary gland and adrenal gland, respectively, through the V1b receptor. In addition, AVP plays a crucial role in blood pressure control by maintaining body fluid retention via the V2 receptor-AQP2 pathway, while AVP stimulates vascular dilatation via the V2 receptor expressed in the vascular endothelium. Hyperosmolarity and decreased plasma volume lead to secretion of AVP from the posterior pituitary, which can bind to the V1a receptor in MD cells and to the V2 receptor in collecting duct cells. The AVP/V1a receptor stimulates the expression of nNOS and COX-2, leading to the production of NO and PGE_2 by MD cells, respectively. Both NO and PGE_2 stimulate renin production from granule cells, and subsequent increases in angiotensin II and aldosterone levels promote water reabsorption. The AVP/V2 receptor enhances translocation of AQP2 to the apical membrane from the cytoplasm. Water reabsorption is further accelerated by the V1a receptor-stimulated renin-angiotensin system. The body fluid is regulated not only by the AVP/V2 receptor system but also by the RAS, which might be enhanced by the AVP/V1a receptor.

ered to be the main cause for the lower BP of V1aR-KO mice, as stated above. Instead, the circulating blood volume in V1aR-KO mice is significantly reduced, possibly due to the reduced responsiveness of adrenocortical hormone secretion. Furthermore, the baroreflex control of HR is significantly attenuated in V1aR-KO mice compared with WT mice. Therefore, extracardiovascular V1a receptors in the adrenal cortex and the baroreflex control center seem to contribute to the basal BP and BP response in V1aR-KO mice (see below for further discussion).

2. CNS effect

In addition to its peripheral action, AVP regulates cardiovascular homeostasis by acting on the baroreflex center and enhancing its sensitivity (256, 301, 454). The baroreflex

enables the rapid adjustment of BP fluctuation. Changes in peripheral BP and blood volume are detected in the arterial baroreceptors and atrial volume receptors, and relayed by vagal afferent fibers to the nucleus tractus solitarius (NTS) (201, 501). AVP appears to act on V1 receptors in the area postrema, a circumventricular organ lacking a blood-brain barrier (201), and enhances the baroreflex function (200, 444). Neurons in the area postrema then project to nuclei that are important for autonomic regulation, including NTS (201).

In V1aR-KO mice or WT mice treated with a selective V1a receptor antagonist, forced increase or decrease of BP by an α_1-adrenergic receptor agonist phenylephrine or by nitrates, respectively, resulted in markedly attenuated HR changes (278). In line with this observation in V1aR-KO mice, the baroreflex sensitivity of AVP-deficient Brattleboro rats was significantly attenuated, indicating the involvement of AVP in baroreflex modulation (230). Electrical stimulation of the hemilateral vagus nerve causes reflex bradycardia, which involves the reflex center, when the nerve was cut at the cervical level and stimulated at the proximal end. This bradycardia response was markedly attenuated in V1aR-KO mice, suggesting a malfunctioning baroreflex arc (383). The V1a receptors are highly expressed in the NTS and area postrema in WT mice (278). Thus V1a receptors in this region may play a crucial role in maintaining the baroreflex control of HR and BP homeostasis.

Centrally administered AVP and related peptides cause complex pressure responses depending on the context. Administration of AVP into the cerebral ventricle resulted in an increase in systemic BP and HR (199, 229, 405). Intracisternal lysine vasopressin (LVP) induced a dose-related decrease in BP and did not change HR (506). Fragments of AVP, AVP(1–6) and AVP(7–9), inhibited the pressor response caused by electrical stimulation of the mesencephalic reticular formation (521). AVP administration into the lateral ventricle increased BP in mice, and this BP increase was blocked by a selective V1a receptor antagonist and blunted in V1aR-KO mice (382). These findings indicate that centrally acting AVP plays a crucial role via the V1a receptor in regulating cardiovascular homeostasis.

3. Water reabsorption and BP regulation

By absorption of water via the V2 receptor-cAMP-AQP2 pathway, AVP maintains body fluid homeostasis. Loss of AVP action on renal water reabsorption results in DI with an excessive volume of diluted urine. To prevent blood volume losses and circulatory failure, intake of an adequate amount of water is essential in patients with DI (292). If DI patients or animal models are supplied with enough water, however, BP remains within the normal range (454). Therefore, at the basal BP level, the renal V2 receptor does not appear to exert any cardiovascular effects. In fact, a pathological increase in serum AVP levels in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) resulted in normal ranges of BP (353, 392). However, in several experimental settings in rats and humans, V2 receptor stimulation by dDAVP or AVP increased not only water permeability but also sodium reabsorption, by directly promoting the activity of the sodium-potassium-chloride cotransporter (NKCC2) in the thick ascending limb of Henle's loop and the amiloride-sensitive epithelial sodium channel (ENaC) in the cortical collecting duct (38, 39, 404, 442, 443, 505).

In contrast to V2 receptor-mediated sodium reabsorption, the V1a receptor is responsible for natriuresis at high doses of AVP (15–50 μg/kg) (404). Although the physiological importance of V1a receptor-mediated natriuretic effects has not yet been determined, renal sodium metabolic control exerted by AVP is likely to result from a combination of opposite responses mediated by the V2 and V1a receptors (38). Luminal AVP has been shown to cause diuresis by inhibiting basolateral membrane V2 receptor-mediated water absorption and chloride conductance (367, 375). The diuretic effect induced by luminal AVP is possibly due to the luminal V1a receptor, although conclusive evidence has not yet been reported.

4. Indirect cardiovascular effects mediated by other hormones

In addition to the direct effects on the heart and vasculature, AVP can regulate cardiovascular function through its interactions with other hormones and control systems. Among these are adrenal hormones (see sect. III*C* for details). The V1a receptor is expressed in the normal adrenal cortex and in hypertrophic and cancer states (53, 196, 258, 474). Both V1a and V1b receptors are found in chromaffin cells of the adrenal medulla, where AVP stimulates catecholamine secretion (184, 195). AVP peptide is found in the adrenal medulla and is believed to stimulate the secretion of adrenocortical and medullar hormones as a paracrine/autocrine hormone (195). In V1aR-KO mice, the secretion of glucocorticoids, corticosterone in rodents, and mineralocorticoid (mainly aldosterone) upon AVP stimulation was significantly attenuated (27, 53, 278). Both corticosterone and aldosterone are important in body fluid and cardiovascular homeostasis and contribute to BP homeostasis through circulating blood volume.

AVP stimulates not only adrenocortical cells but also renal granule cells to promote renin production via the V1a receptor, and subsequently increases serum angiotensin II and aldosterone levels (see sect. III*B* for details). These findings suggest that the V1a receptor-mediated enhancement of the renin-angiotensin-aldosterone (RAA) system may be involved in maintaining plasma volume and BP. **FIGURE 3** summarizes the regulation of body fluids by AVP mainly via the V1a and V2 receptors.

In summary, V1a receptors in multiple tissues and cell types may contribute to BP regulation. In addition to the vascular V1a receptor, AVP acts on extracardiovascular receptors, expressed, for example, in the adrenal cortex and medulla, renal granule cells and collecting duct epithelium, circum ventricular organ, and baroreflex center. The direct effect of AVP on cardiac pathology is not fully understood. A recent report suggests that transgenic overexpression of V1a receptor in cardiomyocytes results in contractile dysfunction in a G_q-dependent manner (300). We also observed that less hypertrophy developed in V1aR-KO hearts compared with those of WT mice, when a pressure load was introduced to mouse hearts by transaortic banding (221). The relevance of these findings in a clinical setting needs to be further explored. The V1b receptors, on the other hand, mediate ACTH secretion by the anterior pituitary and also mediate catecholamine release from the adrenal medulla (244). Whether these V1b receptors participate in the regulation of cardiovascular function by AVP remains to be determined.

B. Renal Function

In the kidney, AVP principally participates in maintaining body fluid homeostasis by regulating water, urea and ion transport, glomerular filtration rate (GFR), and renal blood flow (292). It is well known that AVP exerts its antidiuretic effect by regulating sodium and water transport via the V2 receptor, which is expressed in the basolateral membrane of the thick ascending limb of Henle's loop, distal tubules, and the collecting ducts in the kidney (231). Through the V2 receptors, AVP stimulates the G_s protein and adenylate cyclase to increase intracellular cAMP, which stimulates the translocation of AQP2 and the amiloride-sensitive ENaC in the principal cells of the collecting duct, and thereby increases water reabsorption (237).

In addition to V2 receptor expression, V1a and V1b receptors are also found in the kidney (237). The V1b receptor may be expressed in the inner medulla of the kidney (435), although its functional role remains to be clarified. Several studies have shown that the V1a receptor mediates AVP functions at various sites in the kidney, including the glomerulus, renal medulla, and renal vasculatures (390, 486). Indeed, it has been proposed that the V1a receptor mediates the effects of AVP on renal blood flow, since stimulation with a renal medullary interstitial infusion of a selective V1 receptor agonist, [Phe^2,Ile^3,Orn^8]vasopressin, significantly decreased medullary blood flow in anesthetized renal-denervated rats (364). More importantly, the V1a receptor was also found in the medullary and cortical thick ascending limb of loop of Henle and the cortical, outer medullary, and inner medullary collecting duct (CCD, OMCD, and IMCD, respectively) in the kidney (22, 79, 85, 486, 489), suggesting its involvement in regulating body fluid homeostasis (237). The expression level of the V1a receptor is lower at deeper portions than at shallow portions of the collecting ducts and is not present in the terminal IMCD (320, 486). More specifically, V1a receptor expression in the renal medulla was restricted to the V-ATPase/anion exchanger-1-labeled α-intercalated cells (85). Several studies have suggested that the V1a receptor in the CCD is distributed in the principal and intercalated cells (85), whereas the V2 receptor, AQP2, and ENaC are distributed in the principal cells of the collecting ducts (375) **(FIGURE 4)**.

Tashima et al. (486) investigated the effects of metabolic acidosis and dehydration on the mRNA expression of the V1a receptor along the nephron. Metabolic acidosis increased the mRNA expression of the V1a receptor in the collecting ducts, whereas the mRNA expression of the V2 receptor was decreased by metabolic acidosis. In contrast to metabolic acidosis, dehydration decreased the mRNA expression of the V1a receptor and increased the mRNA expression of the V2 receptor in the collecting ducts. These data suggest the possible functional interaction of V1a and V2 receptors, at least in the collecting ducts; the V1a receptor may regulate the V2 receptor-mediated AVP action in the collecting ducts.

There is also evidence that an AVP-related receptor exists on luminal (apical) membranes in the collecting ducts (22). It was found that urinary AVP suppressed the V2 receptor function via the V1a receptor in the collecting duct. The luminal AVP inhibited V2 receptor-stimulated water and urea permeability in the collecting duct (375), which is probably mediated by the V1a receptor expressed in the luminal membrane of the intercalated cells, suggests that the V1a and V2 receptors play different roles in renal function (486). cAMP accumulation was measured in the collecting ducts in both the presence and absence of AVP in the lumen (375). AVP in the lumen stimulated the V1a receptor and suppressed cAMP accumulation mediated by the basolateral V2 receptors. Measuring luminal AVP-stimulated cAMP accumulation became possible using the isolated tubule perfusion technique. Ando et al. (22) confirmed the presence of another AVP receptor in the luminal membrane of the CCD by measuring the transepithelial voltage and water permeability. Naruse et al. (367) also investigated the effects of luminal AVP on chloride conductance.

Furthermore, Izumi and co-workers (247, 248) reported the following: V1a receptor stimulation resulted in suppression of V2 receptor promoter activity, hypertonicity enhanced V2 receptor promoter activity, and suppression of V2 receptor expression by V1a receptor stimulation was enhanced by hypertonicity. Memetimin et al. (334) reported that low pH enhances V1a receptor stimulation-induced suppression of V2 receptor promoter activity. These findings suggest that the V1a receptor plays a role in maintaining minimal urine flow for renal function by acting against V2 receptor-mediated antidiuresis under chronically dehydrated conditions and that water and electrolyte metabo-

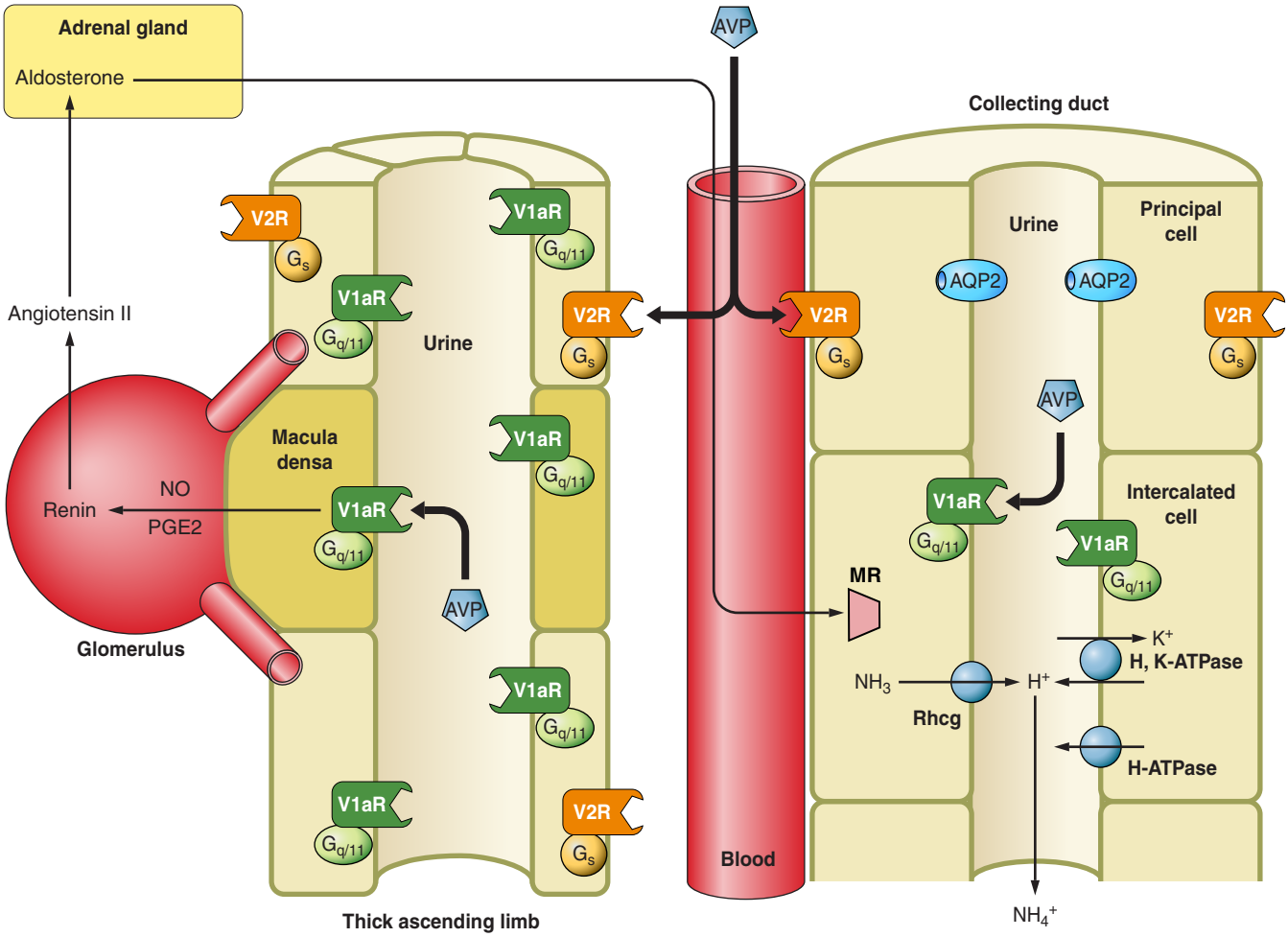


FIGURE 4. Regulation of aldosterone action by the V1a receptor. The V1a receptor in the macula densa, coexpressed with nNOS and COX-2, promotes renin production in the granular cells, which finally stimulate aldosterone production in the adrenal gland. In the intercalated cells of the collecting ducts, aldosterone stimulates H^+-K^+-ATPase and Rhcg expressions and decreases H^+-ATPase abundance. The V1a receptor is required for these actions through normal production of aldosterone. A functional defect in the V1a receptor results in inadequate synthesis of aldosterone in the adrenal gland (hyporeninemic hypoaldosteronism) and inadequate action of aldosterone in the intercalated cell, which finally results in type 4 renal tubular acidosis.

lism may be controlled by the elaborate interaction between V1a and V2 receptors along the nephron. Urinary AVP serves as an intrinsic diuretic by inhibiting V2 receptor-mediated antidiuretic action via activating the V1a receptor (375, 376).

A study with V1aR-KO mice showed that the mutant mice exhibited increased urine volume, lower urine osmolarity, and decreased Na^+ and Cl^- excretion (27). Plasma renin, angiotensin II, and aldosterone levels are decreased in V1aR-KO mice (27, 53). Immunostaining of renin in the granular cells was largely decreased in V1aR-KO mice compared with WT mice, suggesting the presence of hyporeninemic hypoaldosteronism in V1aR-KO mice. To investigate the mechanisms of hyporeninemic hypoaldosteronism in V1aR-KO mice, the mRNA expression of the V1a receptor in the macula densa (MD) cells was examined by in situ hybridization. V1a receptor mRNA was present in the MD cells of WT mice, but not in those of V1aR-KO mice. Nitric oxide (NO) and prostaglandin E_2 (PGE_2) are believed to mediate the signals of the V1a receptor to the glomeruli, and the expression of neuronal nitric oxide synthase (nNOS) and cyclooxygenase-2 (COX-2) was depressed in V1aR-KO mice. The data suggest that the V1a receptor in the MD cells, coexpressed with nNOS and COX-2, participates in RAS by regulating renin production and that the lack of V1a receptors in the MD cells plays a major role in the occurrence of hyporeninemic hypoaldosteronism in V1aR-KO mice (27).

In addition, V1aR-KO mice had lower levels of blood HCO_3^- concentration and carbon dioxide partial pressure (P_{CO_2}), indicating that they undergo metabolic acidosis with respiratory compensation (219, 246). Plasma K^+ concentration was higher in V1aR-KO mice, whereas the urinary pH under basal conditions was lower in V1aR-KO mice than in WT mice (246). Stimulation of urinary acidification by the drinking of NH_4Cl resulted in a decrease in

the urinary pH in both WT and V1aR-KO mice, but urinary pH levels were lower in V1aR-KO mice than in WT mice. The increase in net acid excretion was significantly smaller in V1aR-KO mice because of insufficient ammonium excretion. These findings suggest that V1aR-KO mice exhibit a phenotype of type 4 renal tubular acidosis (RTA), characterized by low BP, reduced renal function, metabolic acidosis, and hyperkalemia, which is known to be caused by hyporeninemic hypoaldosteronism (27). The type 4 RTA may result from defects in the V1a receptor in intercalated cells, which affects the tubular effects of aldosterone.

The expressions of acid base-related transporters were further investigated in the intercalated cells in WT and V1aR-KO mice by Izumi et al. (246). Knockout of the V1a receptor resulted in decreased expressions of H^+-K^+-ATPase, and the Rhesus blood group C glycoprotein (Rhcg) and increased expression of H^+-ATPase. Urine pH was unexpectedly low in V1aR-KO mice, which was thought to result from the activation of H^+-ATPase. However, an old model of nonionic diffusion of NH_3 across the colleting duct membrane could not explain the low urinary ammonium excretion even with the low urine pH observed in V1aR-KO mice. Biver et al. (54) refuted the old nonionic diffusion model by investigating the role of Rhcg as an NH_3 transporter. They found that more than two-thirds of NH_3 was transported via Rhcg and that less than one-third of NH_3 was transported by nonionic diffusion, which was compatible with findings from the study on V1aR-KO mice. V1aR-KO mice showed a low abundance of Rhcg, and the administration of fludrocortisones ameliorated the low urinary ammonia excretion and metabolic acidosis and increased expression of Rhcg. Low expression of H^+-K^+-ATPase in V1aR-KO mice was also ameliorated by the administration of fludrocortisones. Anion exchanger member 1 (AE1) and pendrin expressions were not decreased in V1aR-KO mice. These results suggest that low expressions of H^+-K^+-ATPase, and Rhcg are responsible for the type 4 RTA observed in V1aR-KO mice. Increased expression of H^+-ATPase is thought to be an adaptive change. Thus H^+-ATPase, H^+-K^+-ATPase, and Rhcg are AVP-dependent transporters (246).

Izumi et al. then examined whether these changes in acid base-related transporters can be seen in the intercalated cells. For that purpose, they made a new cell line of rat intercalated cells (IN-IC cells) from SV40 temperature-sensitive large T antigen transgenic rats (539). The IN-IC cells have the V1a receptor, H^+-ATPase, H^+-K^+-ATPase, Rhcg, AE1, and pendrin, but not the V2 receptor, AQP2 or ENaC, suggesting the characteristics of the intercalated cells. These results clearly show that the V1a receptor is localized in the intercalated cells. The cells also have the mineralocorticoid receptor (MR) and 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2). These results revealed for the first time that MR is present in the intercalated cells. MR thus plays a major role related to aldosterone action not only in the principal cells but also in the intercalated cells (366, 504). Aldosterone stimulated the expressions of H^+-K^+-ATPase, and Rhcg and decreased the expression of H^+-ATPase in the IN-IC cells in a dose-dependent manner. To mimic V1aR-KO mice, the V1a receptor mRNA was knocked down by siRNA in IN-IC cells, which abolished the effects of aldosterone on H^+-ATPase, H^+-K^+-ATPase, and Rhcg abundances (246). These results clearly show that deficiency in the V1a receptor results in type 4 RTA, which occurs frequently in patients with diabetic nephropathy (447).

In summary, the role of the V1a receptor can be summarized as *1*) inhibitory regulation of the basolateral V2 receptor-mediated antidiuretic and antinatriuretic action of AVP, *2*) regulation of renin production in the MD cells, and *3*) regulation of aldosterone action on H^+-ATPase, H^+-K^+-ATPase, and Rhcg in the intercalated cells.

C. The Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the maintenance of basal and stress-related homeostasis. Among the peripheral tissues that participate in the HPA axis, V1b receptors are expressed in the anterior pituitary and the adrenal medulla, V1a receptors in adrenal cortex, while the OT receptor is found in a minor population of anterior pituitary cells. Thus the functions of the HPA axis may be modulated at multiple sites by AVP/OT. However, the details of the physiological importance of each receptor have yet to be clarified. In this section, we summarize the in vivo studies on the HPA axis of model animals produced by genetic and pharmacological methods.

The hypothalamus controls the secretion of ACTH from the anterior pituitary by the release of corticotropin-releasing hormone (CRH) and AVP, and ACTH in turn stimulates the secretion of glucocorticoids from the adrenal cortex. Adrenal glucocorticoids, corticosterone in rodents and cortisol in humans regulate a broad spectrum of physiological functions under both basal and stress conditions (25, 292). The sensitivity of the HPA axis to incoming stimuli is modulated by a negative-feedback system, which is inhibited by the glucocorticoids themselves.

For the control of ACTH secretion, CRH and AVP act synergistically on specialized cells, the corticotrophs, in the anterior pituitary gland (9, 77, 165, 177, 502). Although early studies proposed that AVP was the hypothalamic corticotrophin-releasing factor (331), after isolation of CRH from ovine hypothalami (515), this CRH peptide and its rodent and human counterparts proved to be a more powerful ACTH secretagogue than AVP, and it has since been shown to play a major role in the regulation of the HPA axis (7).

ACTH secretion of the anterior pituitary induced by AVP is mediated through the V1b receptor (36, 252). Two kinds of CRH receptors, CRH-R1 and CRH-R2, have been identified thus far (202). Although the functions of CRH-R2 are not yet fully understood, it has been well established that CRH-R1 mediates many anxiety- and depression-like behaviors, as well as CRH-stimulated ACTH release (203). Activated CRH-R1 in the anterior pituitary couples with G_s protein and increases cAMP in cultured anterior pituitary cells (7). On the other hand, the V1b receptor mainly couples with the $G_{q/11}$ protein and activates PLC-mediated phosphatidylinositol turnover and intracellular calcium signaling (298, 308, 415). Although activation of pituitary V1b receptors by AVP in the absence of CRH stimulation does not increase the intracellular cAMP content (7), the synergistic enhancement of CRH-induced ACTH secretion by AVP is mediated through multiple factors, such as the activation of protein kinase C, increase in intracellular calcium, arachidonic acid production, and potentiation of CRH-induced cAMP formation (1). Because direct interactions between GPCRs by forming heterodimeric complexes are known to generate a receptor of altered pharmacological properties from the original homomeric receptors (63, 431), a study was performed to examine the possibility of hetero-oligomerization between CRH-R1 and V1b receptors. The results suggest that they are capable of forming constitutive homo- and heterodimers and that this interaction does not affect the binding properties of the receptors (545). In birds, the cooperative increase in ACTH release from the anterior pituitary gland by CRH and vasotocin (AVT) is conserved and the responsible receptors for this enhancement, CRH receptors and VT2 vasotocin receptors, were shown in a study on chickens to form heteromers under stimulation of both CRH and AVT, but not CRH or AVT alone (340). When cAMP production was examined in cells expressing both CRH receptors and VT2 receptors, coapplication of CRH and AVT resulted in a significant increase in cAMP production over that with CRH alone, indicating functional heterodimer formation (340).

Although the entire mechanism of the functional synergism between CRH and AVP in ACTH secretion needs further investigation, the involvement of the V1b receptor in AVP-induced ACTH release from the anterior pituitary has been further confirmed in recent studies, which employed newly developed pharmacological tools selective for the V1b receptor over other receptor subtypes and V1b receptor knockout (V1bR-KO) mice (453, 484). ACTH and glucocorticoid responses under basal or stress conditions in animals treated with drugs or mutant animals (V1bR-KO mice and Brattleboro rats) are summarized in **TABLES 2–4**.

SSR149415 is the first selective nonpeptide V1b receptor antagonist with nanomolar affinity for both human and rat V1b receptors (452). SSR149415 is now known to have an affinity to the human OT receptor (189). Intraperitoneal or oral administration of SSR149415 resulted in a decrease in AVP-induced ACTH secretion in conscious rats. Potentiation of CRH-induced ACTH secretion by AVP was also decreased by oral SSR149415 administration (452). Another V1b receptor antagonist, ORG52186, also termed Org, which was recently identified, is able to bind to the human V1b receptor with high affinity and exhibits >1,000-fold selectivity over the other members of the AVP receptor subfamily and a broad range of other receptors, ion channels, transporters, and enzymes (103).

In addition to these pharmacological studies, genetically modified mice lacking the V1b receptor are valuable. In cultured anterior pituitary cells derived from V1bR-KO mice, ACTH release was not induced by up to 10 μM of AVP treatment, whereas AVP induced significant ACTH release in cells from WT mice. CRH-induced ACTH release was comparable between WT and V1bR-KO mice (484). Corresponding to the results on the primary culture of anterior pituitary cells, an in vivo study with V1bR-KO mice and V1b receptor antagonists also found that blunting the AVP/V1b receptor signal resulted in a suppressed plasma ACTH response to the AVP stimulation, which consequently

Table 2. *Hypothalamic-pituitary-adrenal axis responses at basal condition and under CRH/AVP stimulation*

Antagonist/KO/BB Rat	Basal or CRH/AVP stimulation	ACTH*	Glucocorticoid+	Reference Nos.
V1bR-KO	Basal	↓ or →	↓ or →	313, 484, 533
	CRH	→	→	
	AVP	↓		
	CRH + AVP	↓		313
Org to rat	–	→	→	463
	AVP	↓	↓	
BB rat	Basal	→	↓ or →	74, 548, 550
	CRH	↓	→	
	ACTH		↓	

Relative differences from control (no drug treatment or WT) in serum ACTH (*) and glucocorticoid (+) concentrations are indicated by arrows. Org, V1b antagonist ORG52186.

Table 3. *Hypothalamic-pituitary-adrenal axis responses to a variety of acute stress conditions*

Antagonist/KO/BB Rat	Stimulation (Stressor)	ACTH*	Glucocorticoid+	Reference Nos.
V1bR-KO	Forced swim (0.5–10 min)	↓	↓ or →	313, 424, 429, 430, 468, 469, 484
	Insulin	↓	↓	
	Restraint (30 min)	→	→	
	Mild restraint	↓	→	
	30 min or 4 hour after LPS	↓ or →	↓ or →	
	Ethanol (i.p.)	↓	↓	
	Novel environment	↓	↓	
	Fluoxetine	↓	↓	
	Desipramine	↓	↓	
	Shaker stress	↓	→	
	Osmotic stress (water deprivation)	→	↓	
Org to WT mice	Restraint (30 min)	↓	↓ or →	430
	Forced swimming (5 min)	↓ or →		
Org to V1bR-KO	Forced swimming (5 min)	→	→	
BB rat	Forced swim (up to 60 min)	↓	→	126, 548, 552
	Insulin	↓	→	
	Restraint (1–60 min)	↓	↓	
	One hour after LPS	↓	→	
	Morphine (s.c.)	↓	↓	
	NMDA (i.v.)	→	→	
	Kainate (i.v.)	→	→	
	Hypertonic saline (i.p.)	↓	→	
	Saline (i.v.)	→	→	
	Egg white injection	↓	→	
	Ether inhalation (8 min)	→	→	
	Novelty stress	↓	→	
	Elevated plus-maze (5 min)	↓	→	
	Ulcerogenic cold-immobilization	↓	→	
	Social avoidance (8 min)	→	→	
	Foot shock	→	→	
	Aggressive interaction (10 min)	↓	↓	
V1 antagonist[1] to rat	Ethanol (p.o.)	↓	↓	291, 463, 554
V1b antagonist[2] to rat	Foot shock	↓	↓	
Org to rat	Restraint (60 min)	↓	→	
	Noise (96 dB for 10 min)	→	→	
	LPS	↓	→	

Relative differences from control (no drug treatment or WT) in serum ACTH (*) and glucocorticoid (+) concentrations are indicated by arrows. Org, V1b antagonist ORG52186; [1], [d(CH(2))(5)Tyr(Me)-AVP] (1.0 μg/kg); and [2], SSR149415 (1 or 10 mg/kg).

led to a decreased corticosterone level (484) **(TABLE 2)**. These findings indicate that AVP-stimulated ACTH release via V1b receptors cannot be fully compensated for by other stimulatory signals on corticotrophs in vivo, and that blockade of the AVP/V1b receptor signal does not affect the CRH/CRH-R1 effect on the ACTH release. It should be mentioned that the synergistic increase in ACTH secretion by coapplications of both AVP and CRH is lost in mice lacking the V1b receptor (313).

Although AVP and CRH play a crucial role in the control of the HPA axis under conditions of stress, the extent of the contributions of these peptides in regulating the HPA axis under basal conditions remains unclear. While basal levels of corticosterone in CRH-R1 KO mice were below the assay detection limit, the basal level of ACTH in CRH-R1 KO mice was indistinguishable from that of WT controls (356). The plasma concentration of AVP, but not of OT, was significantly elevated in CRH-R1 KO mice, which is believed to be a compensatory mechanism to maintain basal ACTH secretion and HPA system activity under the CRH/CRH-R1 signal-deficient condition (356). Previous studies reported reduced basal ACTH and/or corticosterone levels in Brattleboro rats (74), whereas

Table 4. *Hypothalamic-pituitary-adrenal axis responses to a variety of chronic stress conditions*

Animals	Chronic (Repeated) Stress	Stimulation (Stressor)	ACTH Response*	Glucocorticoid Response+	Reference Nos.
V1bR-KO	Restraint	Acute restraint	↓	→	313, 429, 469
	Forced swim	Forced swim	↓	→	
	Novel environment	Novel environment	↓	↓	
	Shaker stress	Shaker stress	→	→	
BB rat	Morphine (10–100 mg/kg) injections	The time the last injection was expected		↑	126, 550
		Four hour after the last saline injection	↓	↓	
		Four hour after the last morphine injection	→	↑	
	Restraint		↓	→	
Rat	Restraint	White noise exposure (10 min) after single administration of SSR149415	↑	→	87
	Restraint and administrations of V1 or V1b antagonist[1]	Hypertonic saline (1.5 N NaCl, 1.5 ml/100g)	→	→	
	Restraint and administrations of SSR149415	AVP (100 ng i.v.)	↓	↓	
	Restraint	AVP and Org	↓	↓	462
		Acute restraint and Org	→	→	
		LPS and Org	↓	→	
		Noise (96 dB, 10 min) and Org	↓	→	
	Single 60 min restraint	Noise (96 dB, 10 min) and Org	↓	→	

Relative differences from control (no drug treatment or WT) in serum ACTH (*) and glucocorticoid (+) concentrations are indicated by arrows. Org, V1b antagonist ORG52186;[1], V1 and V1b antagonists are dGly[Phaa1,D-tyr(et), Lys, Arg]VP, and SSR149415, respectively.

others reported no significant change of these parameters in Brattleboro rats (126, 343, 548). In V1bR-KO mice, only corticosterone was studied and was not decreased (533). Thus controversy remains regarding the functional role of AVP in maintaining the basal condition of the HPA axis.

In addition to AVP, it has been suggested that OT is involved in stimulating ACTH release from the anterior pituitary gland, where both OT receptors and V1b receptors are expressed (445). When we examined the possibility that ACTH secretion is stimulated by AVP/OT receptor family members other than the V1b receptor in a study using V1bR-KO mice, we found OT stimulated ACTH release in WT and V1bR-KO mice (361). OT-induced ACTH release was significantly inhibited by the V1b receptor antagonist SSR149415 and by the OT receptor antagonist CL-14–26 in WT mice. In addition, cotreatment with SSR149415 and CL-14–26 inhibited OT-induced ACTH release to the control level in WT mice. In V1bR-KO mice, OT-induced ACTH release was significantly inhibited to the control level only by CL-14–26. These results suggest that OT induces ACTH release via OT and V1b receptors, whereas AVP induced ACTH release only via V1b receptors **(FIGURE 5)**.

Although CRH is the primary ACTH secretagogue (7, 165, 177), the influence of the AVP/V1b receptor on the HPA axis response becomes more significant under certain stress conditions (8, 310, 429). Blockade of the V1b receptor and CRH-R1 by the antagonists SSR149415 and CP-154,526, respectively, is effective for diminishing the ACTH response to stress. The simultaneous blockade of both CRH-R1 and

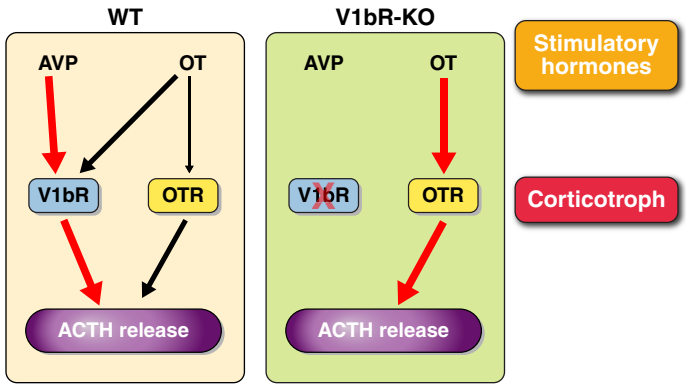


FIGURE 5. Mutual regulation of ACTH release from the anterior pituitary gland by AVP and OT stimulation. AVP stimulates ACTH release via the V1b receptor in the anterior pituitary glands. OT also stimulates ACTH release via the OT receptor in addition to the V1b receptor. Under the V1b receptor-deficient condition, OT mediates ACTH release via the OT receptor, whereas AVP does not.

V1b receptors abolishes the ACTH response to various stressors, such as ether exposure, forced swimming, and restraint (411).

It has been reported that the expression of OT receptors and V1b receptors in the anterior pituitary is increased in Brattleboro rats (361), whereas CRH levels in the hypothalamus remain unchanged (274). Also, the plasma level of OT, which has a modest affinity for the V1b receptor and is known to mediate ACTH release via the V1b receptor (307, 445), is elevated in Brattleboro rats (57). Therefore, OT at high concentrations can activate OT receptors present in pituitary corticotrophs to release ACTH in Brattleboro rats (361), contributing to the ACTH response to stress stimulation.

A number of studies using receptor antagonists or mutant animals (V1bR-KO mice and AVP-deficient Brattleboro rats) have shown that inhibition of AVP action can reduce ACTH and corticosterone responses to acute stress **(TABLE 3)**. Our study with V1bR-KO mice showed that the ACTH and corticosterone responses to acute stress due to a forced swim test were reduced (484). The results of studies on hormone secretion in the HPA axis in response to stress stimuli depend highly on the experimental settings, including the amount of stress and the time points of blood collection. In another forced swimming test, plasma levels of corticosterone, but not ACTH, were elevated 105 min after the onset of stress only in Brattleboro rats (551). Other types of acute stress have also been examined (313, 314, 424, 430, 462, 468, 469, 554). In insulin-induced hypoglycemia stress, but not acute restraint stress, an increase in plasma ACTH and corticosterone levels was attenuated in V1bR-KO mice (313). Acute administration of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) has been shown to activate the HPA axis. Administration of an SSRI (fluoxetine, 10 mg/kg) and a TCA (desipramine, 10 mg/kg) resulted in significantly lower plasma ACTH and corticosterone levels in male and female V1bR-KO mice (468). The ACTH responses to other acute stressors, such as mild restraint, forced swimming, and changes in environmental stress, were also significantly attenuated in V1bR-KO mice (469). In osmotic stress induced by water deprivation, both ACTH and corticosterone were increased in WT and V1bR-KO mice, while the increase in corticosterone was significantly lower in V1bR-KO mice than in WT mice (424). ACTH, but not corticosterone, levels are decreased after blockade of the V1b receptor or in V1bR-KO mice under several stress conditions. This discrepancy between ACTH and corticosterone levels may be partly explained by corticosterone secretion by a system other than the AVP-ACTH system, and possible involvement of sympathetic modulation (140), although this hypothesis needs to be experimentally proven.

The V1b receptor antagonist Org suppressed increases of ACTH secretion evoked by acute restraint, lipopolysaccharide (LPS) administration, and acute noise stress (103, 462). Water deprivation for 24 h also increased the plasma corticosterone level, and this increase was significantly attenuated in V1bR-KO mice (424). Thus the profound reduction in plasma ACTH levels following acute stress demonstrates that the loss of the AVP/V1b receptor signal cannot be compensated for by CRH or other factors such as OT (313, 314, 468, 469). It is important to emphasize that in some species (e.g., sheep and horse), AVP rather than CRH appears to be the main ACTH secretagogue (17, 143). Alexander et al. (17) suggested that in horses, AVP is the primary stimulator for ACTH release both before and during hypoglycemia. CRH release then augments corticotroph responses to AVP (17, 143). In addition, in sheep, insulin-induced hypoglycemia markedly increased AVP and, to a lesser extent, CRH concentrations in portal plasma. The marked alteration of the CRH:AVP molar ratio under stress suggests that AVP may be an important ACTH secretagogue in the sheep (143).

Previous studies using Brattleboro rats have repeatedly demonstrated the importance of AVP in driving ACTH secretion under a variety of stress conditions (126, 343, 548, 550–552). In Brattleboro rats, the resting hormone levels of ACTH and corticosterone, as well as their circadian rhythmicity, did not differ from heterozygote controls (548). Increases of ACTH and corticosterone in response to volume load, restraint, or aggressive attack were decreased in Brattleboro rats. The stress-induced increase in the ACTH level, but not corticosterone level, was significantly impaired in Brattleboro rats after novelty, elevated plus maze, forced swim, hypoglycemia, ulcerogenic cold immobilization, LPS administration, hypertonic saline injection, and egg white injection (548). Stressors such as isolation, ether inhalation, and foot shocks did not reveal any difference between the two rat groups (548). In rats, the acute administration of chemicals such as morphine and excitatory amino acids activates the HPA axis (69, 76, 552). Morphine administration in Brattleboro rats produced a small yet significant reduction in the elevations of both ACTH and corticosterone levels (126). After repeated administration of morphine, ACTH levels of control rats were significantly elevated 16 h after the last morphine injection, with a smaller rise in Brattleboro rats (126). The intravenous administration of *N*-methyl-D-aspartate (NMDA, 5 mg/kg) or kainate (2.5 mg/kg) elevated the ACTH and corticosterone levels at 5 min in controls, but not in Brattleboro rats (552). In feedback regulation of the HPA axis, Brattleboro rats showed a higher level of dexamethasone-induced suppression of the corticosterone response, which was induced by restraint stress. Finally, higher basal levels of CRH mRNA were detected in the hypothalamic PVN of Brattleboro rats (343).

There have been various studies on the role of AVP in HPA axis regulation during chronic stress **(TABLE 4)**. In studying the responses to chronic stress, the initial increase in ACTH/corticosterone upon the first stressor was compared with following responses to the same (homotypic) stressor after repeated stress exposure. In chronic stress, the HPA axis usually adapts to the stress, and the ACTH/corticosterone responses to later homotypic stressors become smaller for some stressors (restraint and cold stress), but stay the same for some stressors (foot shock) (6). Another strategy to clarify the effect of chronic stress involves the use of novel (heterotypic) stress as the last stress.

Chronic stress such as repeated restraint increased AVP transcription in the parvocellular neurons and immunoreactive AVP signals in the rat median eminence, whereas CRH transcription increased only transiently upon the initial stress, while CRH immunopositive signals did not change even though corticosterone responses to the final restraint stress were maintained (9, 108, 318). Together with the fact that after chronic stress a good correlation was detected between the number of the V1b receptor binding sites in the pituitary and ACTH responsiveness (6), AVP, rather than CRH, has been postulated as the primary regulator of the ACTH responses during chronic stress.

The role of AVP and the V1b receptor in chronic stress has been extensively examined using receptor antagonists, Brattleboro rats, and V1bR-KO mice. Depending on the nature of the stress employed and on the animal species, some, but not all, ACTH responses are reduced by the ablation of AVP and the V1b receptor system, suggesting the active role of the V1b receptor under these conditions **(TABLE 4)**. Notably, however, the reduced ACTH responses induced by blocking or deleting the V1b receptor are compensated for by an unknown mechanism, and do not lead to a reduction of corticosterone under different stress conditions except for the change in environment stress **(TABLE 4)**. This discrepancy between ACTH and corticosterone levels was also found in a study on acute stress **(TABLE 3)**. Therefore, studies employing V1b receptor blockade or V1bR-KO mice might shed light on the complex interactions between ACTH and other secretagogues of glucocorticoid hormones under conditions of acute and chronic stress. The role of the V1b receptor in HPA activation is described in detail in the excellent review by Roper et al. (429).

Our understanding of the role of AVP in the regulation of HPA function has advanced significantly over the last 50 years. Despite the controversies of the early years, there can now be little doubt that AVP plays a fundamental role in driving ACTH secretion and that it acts, at least in part, synergistically with CRH. AVP contributes to the regulation of basal ACTH release and to the response to various stressors. The possibility that dysfunction of the vasopressinergic system within the HPA axis may contribute to disease pathology is receiving increasing attention, with emerging data pointing to a potential role for AVP receptor antagonists in the treatment of depression and certain anxiety states (see below).

D. Adrenal Function

In addition to the central production of AVP in the hypothalamus, it has been suggested that AVP is synthesized from its precursor, prepro-AVP, in several tissues, including the ovaries, testes, uterus, thymus, pancreas, and adrenal gland (379). Some studies demonstrated that, in the adrenal gland, AVP is synthesized and secreted by chromaffin cells in the medulla or chromaffin cells scattered throughout the cortex, with prominent concentration in the zona glomerulosa (166, 414). The immunoreactivity of AVP in the medulla was detected in cells containing epinephrine and norepinephrine (NE) or epinephrine alone, depending on the species (205). AVP V1a, V1b, and V2 receptor and OT receptor mRNAs have been detected in the mouse adrenal gland by RT-PCR (53). The V1a receptor is predominant in the adrenal cortex and is also detected in the medulla (53). On the other hand, the V1b receptor is expressed in the adrenal medulla, especially in chromaffin cells (166, 185, 215). Thus it appears that AVP participates in the regulation of adrenocortical and medullar functions through an autocrine/paracrine mechanism in the adrenal gland (166, 183, 195), although the production of AVP in the peripheral tissues should be carefully examined via mRNA and protein levels.

In the adrenal cortex, by acting on the V1a receptor subtype, AVP exerts two main effects: it increases the mitogenic activity of the zona glomerulosa (ZG) in the rat adrenal cortex (398) and stimulates aldosterone and glucocorticoid secretion in mice, rats, cats, calves, and humans (53, 402). AVP administration promotes both hypertrophy and hyperplasia of adrenal cortical parenchymal cells in rats (329, 398), resulting in enlargement of the ZG (166). Treating rats with an AVP V1 receptor antagonist strongly depressed the growth of the adrenal cortex (183, 330), suggesting the involvement of the V1 receptor in the AVP-stimulated cell proliferation in vivo. Pharmacological studies also indicated that the V1a receptor is responsible for the effect of AVP on the adrenal cortex (50, 196). The direct effect of AVP was further confirmed by an in vitro study with primary culture of glomerulosa cells, in which AVP enhanced the rate of mitotic activity (166, 329).

In addition to its mitogenic effect, several studies have demonstrated that AVP is capable of stimulating aldosterone secretion. Hilton et al. (216), in a study that employed direct arterial perfusion in dogs, first suggested that LVP stimulates the secretion of aldosterone by the adrenal glands and that this effect is mediated through direct stimulation by

LVP. Several experiments conducted with Brattleboro rats indicate that aldosterone secretion is decreased in these animals, indicating that AVP from the hypothalamo-pituitary complex is directly involved in the regulation of aldosterone secretion, independent of its action on ACTH secretion. Several subsequent studies conducted in vitro confirmed that AVP can directly stimulate aldosterone secretion, not only in rat adrenal glomerulosa cells (217) but also in humans (196), mice (53), and other species.

AVP-stimulated aldosterone release from cultured cells isolated from mouse adrenal glands was inhibited by the V1a receptor antagonist OPC-21268 and was blunted in the cells from V1aR-KO mice, indicating that AVP stimulates aldosterone secretion via the V1a receptor (53). Furthermore, the plasma aldosterone level was decreased in V1aR-KO mice, suggesting that the AVP/V1a receptor signal plays a crucial role in regulating aldosterone release from the adrenal cortex in vivo as well as in vitro (27, 28, 53). The lower plasma aldosterone level observed in V1aR-KO mice may be caused not only by the blunted AVP/V1a receptor action in the adrenal cortex but also by the suppressed RAS activity in these mice (28).

Endogenous glucocorticoids are secreted by the adrenal cortex under the control of ACTH from the pituitary gland, which is regulated by AVP produced in the hypothalamus. In addition, AVP is known to directly stimulate glucocorticoid secretion via the V1a receptor in the human adrenal cortex (196, 401). In humans, Hensen et al. (213) showed that AVP administration, which led to an insignificant increase in the plasma ACTH level, significantly increased the plasma cortisol level. Moreover, peripheral administration of AVP was found to cause ACTH secretion, which resulted in glucocorticoid secretion from the adrenal cortex, when the plasma AVP level was above the physiological range (213). Thus AVP can stimulate glucocorticoid secretion directly through the adrenal V1a receptor and indirectly through ACTH secretion (24, 166, 176). Pathophysiological studies have also revealed that Cushing's syndrome, which is caused by ACTH-independent tumors or nodular adrenal hyperplasia, can be accounted for by over-responsiveness to AVP, leading to hypercortisolism (226). There have been several reports suggesting that such tumors may overexpress a eutopic V1a receptor or express a mutated form of the V1a receptor exhibiting oversensitivity to AVP (166, 284, 400). Thus AVP is involved in regulating not only the cell proliferation of glomerulosa cells but also aldosterone and glucocorticoids secretion via the V1a receptor in the adrenal cortex. Loss of the V1a receptor in mice accelerated age-related fluorescent deposits, called "lipofuscin," in the adrenal cortex **(FIGURE 6)**, although the mechanism of this deposit formation and its relationship to the V1a receptor needs to be elucidated.

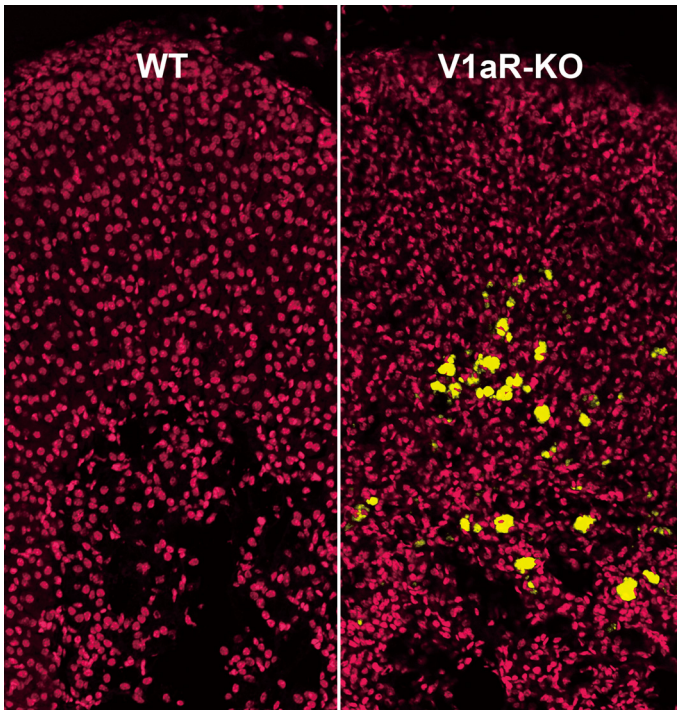


FIGURE 6. Fluorescence images of the adrenal cortex in wild-type (WT) and V1aR-KO mice. Markedly enhanced deposits of the autofluorescent substance lipofuscin, one of the so-called "aging" pigments, are seen in the adrenal gland at 8 wk of age in V1aR-KO mice, but not in age-matched WT mice. Autofluorescent was detected under blue fluorescence light excitation, and signals were pseudo-colored in yellow. Cellular nuclei were stained red with TO-PRO-3.

In the adrenal medulla, synthesis and secretion of AVP is stimulated by neurotransmitters (acetylcholine) or neuropeptides such as CRH (379), and the resulting AVP then stimulates catecholamine release (166, 195, 261). Both V1a and V1b receptors are expressed in the adrenal medulla. Whereas the V1a receptors have been suggested to be expressed in nonparenchymal cells, such as blood vessel walls (166), the V1b receptor mainly present in chromaffin cells is involved in catecholamine secretion (166). The functional role of the V1b receptor in the adrenal medulla under stress conditions was investigated by analyzing the plasma catecholamine levels in V1bR-KO mice. Basal plasma levels of catecholamine such as epinephrine, NE, and dopamine (DA) did not differ between WT and V1bR-KO mice (244). Chronic isolation stress increased plasma catecholamine levels in WT mice, as observed in rats (31), but not in V1bR-KO mice (244). When animals were exposed to acute forced swimming stress, the blood epinephrine level was significantly increased in WT mice, but less so in V1bR-KO mice (244). These results suggest that the AVP/V1b receptor pathway may participate in the regulation of plasma catecholamine levels by directly promoting catecholamine release by the adrenal medulla under stress conditions in vivo.

Thus AVP is one of the autocrine/paracrine regulators of adrenal functions. The adrenal influence may be mediated

in part via pituitary AVP and in part via the local production of AVP. The endogenous AVP secreted by the adrenal medulla is controlled by various physiological factors such as neuromediators (including acetylcholine) released by the splanchnic nerve. AVP may then stimulate the medulla V1b receptors involved in catecholamine and neuropeptide secretion (CRH and ACTH) (328). Functional interaction between AVP and CRH receptors has recently been suggested from the experimental finding that simultaneous stimulation of adrenal medullary cells with AVP and CRH could induce synergistic catecholamine release (358). By dispersing through the adrenal cortex via the medullary ray (167), AVP also regulates the growth of ZG and the secretion of steroids. All possible autocrine and paracrine effects of AVP in the adrenal gland have been summarized in two reviews that discussed the nature, function, and localization of the different AVP receptors found in the adrenal gland (166, 195).

E. Lipid Metabolism and Protein Synthesis

AVP not only regulates water and electrolyte homeostasis through V2 receptors but also modulates the balance of other metabolic functions, such as cellular growth and proliferation, protein turnover, lipid metabolism, and glucose handling, mainly through V1a or V1b receptors. This section and the following sections deal with a range of metabolic functions of AVP and OT.

1. Protein synthesis and turnover

AVP promotes cell proliferation and/or growth by stimulating protein synthesis in several types of cells, such as Swiss 3T3 fibroblasts (123, 432), vascular endothelial and smooth muscle cells (172), cardiomyocytes (221, 363, 536), and others (43, 335, 397, 485). It has been demonstrated in a study using cells engineered to express recombinant receptors that the human V1a receptor, but not the V2 receptor, promotes cellular mitogenic signal transduction and [^{3}H]thymidine uptake (498). When the structural requirements for [^{3}H]thymidine uptake were examined by comparing V1a and V2 receptors, it was determined that the cytoplasmic COOH terminus of the V1a receptor is necessary for the stimulation of DNA uptake by AVP (498). In addition to these diverse functions, AVP is pathophysiologically involved in promoting cell proliferation. In vitro studies with mesangial cells demonstrated that AVP stimulated the production of extracellular matrix (ECM) proteins, such as type IV collagen, which may contribute to the glomerular remodeling and ECM accumulation that leads to glomerular diseases (478). AVP also stimulates the growth of carcinosarcoma cells. After Brattleboro rats were inoculated with Walker 256 cells (derived from rat breast carcinoma), carcinosarcoma grows less intensely and infusion of exogenous AVP intensified tumor growth (267). In many cases, these effects of AVP are mediated by receptors comparable to the V1a receptor subtype (221, 449, 540). Our study showed that AVP-induced cardiomyocyte hypertrophy was suppressed in primary culture from V1aR-KO mice, confirming the involvement of the V1a receptor in cell proliferation (221). In the cellular model of cardiomyocyte hypertrophy, AVP promotes translation of the transcription factor GATA-4 through PKC in H9c2 ventricular myocytes (455). Since the V1a receptor is widely expressed in various malignant cells, including neuroendocrine tumors (377) and small cell lung cancer (SCLC) (319), the AVP/V1a receptor axis may represent a novel target for new tumor therapies.

AVP is reported to promote not only cell proliferation and growth but also organ regeneration (372, 508). Liver regeneration after partial hepatectomy was significantly inhibited in Brattleboro rats that were deficient of AVP (434) or rats treated with the V1a antagonist (372). Administration of AVP into Brattleboro rats after partial hepatectomy increased hepatic DNA and protein synthesis and restored hepatic regeneration (434), supporting the idea that AVP controls liver cell proliferation and growth in vivo as well as in vitro. During liver regeneration, AVP stimulates the progression of the cell cycle of the hepatocytes by activation of NF-κB and cyclin (D1 and A), which contributes to liver mass restoration in rats (372). In sheep livers, however, the V1a receptor is absent. Thus the role of AVP in liver cell proliferation is not conserved in all mammals. On the other hand, AVP has direct proliferative activity and indirect growth inhibiting effect on the regenerating rat adrenal cortex (508).

When we investigated the functional role of the V1a receptor in regulating hepatocyte proliferation and growth using V1aR-KO and WT mice, a number of V1aR-KO mice died within 24 h after a two-thirds hepatectomy (Tanoue, unpublished data), whereas most WT mice survived a partial hepatectomy and their livers were completely restored to their initial mass within a few days, as observed in control rats (372, 434). Among the biochemical markers studied in mice, blood ammonia levels were significantly higher in V1aR-KO mice than those in WT controls, but most other parameters, including AST and ALT, in V1aR-KO mice were indistinguishable from WT mice (219). The higher blood ammonia levels in V1aR-KO mice accompanied higher serum 3-methylhistidine levels, a marker of muscle protein breakdown (546), under a feeding, but not fasting, condition (219). The total amount of amino acids in serum was decreased in V1aR-KO mice under a feeding, but not fasting, condition. The analysis of amino acids in V1aR-KO mice revealed accelerated metabolism of glycogenic amino acids (tyrosine, serine, aspartic acid, methionine, threonine, arginine, valine, leucine, and isoleucine) in muscle tissue. In particular, the decreases in branched-chain amino acids, such as isoleucine, leucine, and valine, support the promotion of protein breakdown in muscle. In addition, an am-

monia tolerance test demonstrated that after oral administration of ammonium chloride, blood ammonia levels remained significantly higher in V1aR-KO mice compared with those in WT mice. When hepatic function was further examined, indocyanine green (ICG) clearance was significantly decreased in V1aR-KO mice. Although the mechanisms for the reduced ammonia tolerance and reduced ICG clearance in V1aR-KO mice remain to be fully clarified, these may be due to decreased hepatic perfusion pressure and reduced intrahepatic circulation, secondary to the lowered systemic BP and reduced systemic circulating blood volume in V1aR-KO mice. The increases in myofibrillar protein degradation and accompanying ammonia production may contribute at least in part to the development of hyperammonemia (219). Taken together, it appears that AVP not only helps promote protein synthesis but also regulates levels of by-products of protein degradation, and blockade of the V1a receptor leads to altered protein metabolism, seen in such conditions as hyperammonemia.

2. Lipid metabolism

AVP participates in the regulation of lipid metabolism through a range of central and peripheral actions. In the CNS, AVP is reported to stimulate sympathetic nerve activity (170, 382), and consequently affects lipid metabolism in peripheral tissues such as liver and fat. AVP also participates in lipid metabolism of adipose tissues directly and indirectly by stimulating several hormone secretions (483). In fat cell lipolysis, triglycerides are cleaved by lipase, and fatty acids and glycerol are released (528). Rofe and Williamson (427) suggested that, in starved rats, AVP affects fatty acid release from adipose tissue by a direct antilipolytic effect. In contrast, depending on the feeding status of the animal and the experimental conditions, AVP and LVP stimulate lipolysis and increase the release of free fatty acids (FFAs) (393, 520, 541). Further involvement of AVP in regulating the supply of energy substrates is suggested by the finding that AVP increases circulating glucose levels by stimulating glucagon release from pancreatic islet cells and by promoting glycogenolysis and gluconeogenesis in the liver (211). These findings imply that AVP regulates lipid metabolism not only through the regulation of lipolysis in adipose tissue but also through the supply of energy substrates, such as glucose.

One consequence of affecting lipid metabolism is a change in the homeostasis of body temperature. AVP is known to regulate the body temperature as one of the main endogenous antipyretic molecules acting in the CNS (see sect. IV). In regard to the peripheral actions of AVP, one study found that the V1a receptor was widely expressed in metabolic tissues, such as the heart, liver, kidney, skeletal muscle, and both brown and white adipose tissues (BAT and WAT), whereas the V1b receptor was only expressed in WAT, and the V2 receptor was not detected in adipose tissues (218). When starved rats were treated with AVP, blood ketone bodies and FFAs decreased (427). The effects of V1a receptor deficiency on lipid metabolism were studied with V1aR-KO mice (218). The blood level of glycerol was higher in V1aR-KO mice than in control WT mice under the feeding condition, whereas ketone bodies increased in V1aR-KO mice after 24 h of fasting. Under the fasting condition, blood triacylglycerol (TG) and FFA levels of V1aR-KO mice were lower than those in WT mice, indicating increased catabolism of lipids in V1aR-KO mice. Furthermore, tandem mass spectrometry measurements revealed that the profiles of serum carnitine and acylcarnitines were altered in V1aR-KO mice under both feeding and fasting conditions. Since the levels and patterns of specific acylcarnitine molecules in serum reflected the acylation states of the cytosolic carnitine pool and of the mitochondrial coenzyme A pool (47, 412), the altered profiles of serum carnitine and acylcarnitines in V1aR-KO can be interpreted as a consequence of the promoted β-oxidation under the V1a receptor-deficient condition (218). Also, increased serum-free creatinine level, altered kidney function, and hormonal condition in V1aR-KO mice may have an influence on serum acylcarnitine levels (27, 66, 218, 412). In agreement with this V1aR-KO study (218), AVP stimulation on isolated rat hepatocytes inhibits the ketogenesis of oleates and stimulates their esterification, demonstrating the inhibition of β-oxidation of fatty acid by AVP (470).

In terms of the modulation of lipolytic activity by AVP, an in vitro assay using brown adipocytes showed that a larger cAMP response was evoked by isoproterenol treatment in V1aR-KO mice than in WT mice. Correspondingly, isoproterenol-induced lipolysis was promoted in the brown adipocytes from V1aR-KO mice compared with WT mice. Therefore, the V1a receptor is necessary for the proper responsiveness of BAT to β-adrenergic receptor agonists (218). AVP increases the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in human adipocytes and has been shown to directly inhibit forskolin- and isoproterenol-induced lipolysis (537). In addition to an increase in forskolin- and isoproterenol-induced lipolysis in V1aR-KO mice, the phosphorylation of Akt by insulin is significantly reduced in the adipocytes of V1aR-KO mice compared with WT mice, indicating that insulin signaling is suppressed in the adipocytes of V1aR-KO mice (218). It is known that kinases involved in insulin signaling, such as Akt and p70S6 kinase, can be activated by AVP via transactivation of the EGF receptor-PI_3-kinase pathway in mesangial cells (175). AVP can thus modulate lipolysis indirectly by affecting insulin signaling in the adipocytes. Studies with V1aR-KO and WT mice have shown that the relatively lower concentrations of TG in V1aR-KO mice are caused by enhanced lipolysis that is at least partially a consequence of the increased sensitivity of isoproterenol-mediated lipolysis and resistance to insulin-mediated inhibition of lipolysis. As a consequence, glycerol concentrations are increased in V1aR-KO mice; however, FFAs are reduced because of a simultaneous enhancement

of β-oxidation (219). Because V1aR-KO mice are glucose intolerant and resistant to insulin-mediated glucose uptake (26), it can be speculated that the hypermetabolism of fat is a compensatory mechanism for the reduced capacity to use glucose as an energy source.

On the other hand, AVP increases the efflux of bile salts, such as taurocholate, from hepatocytes (173). In agreement with this finding on the role of AVP in bile salt release, V1a receptor deficiency in mice resulted in an increase in the total bile acid level in blood, and an enlargement of the cholecyst (219). No apparent sign of liver dysfunction was evident in the blood chemistry test of V1aR-KO mice, and no obstruction of extrahepatic biliary ducts was observed. Therefore, it is not certain at this point why the total bile acid level is higher in V1aR-KO mice. However, it has been suggested that the increased level of cholesterol and taurine in V1aR-KO mice can explain the increased level of bile acid (218). Otherwise, a decrease in the ICG elimination rate in V1aR-KO mice may indicate that the ability to transfer bile acid out of hepatocytes is altered in V1aR-KO mice. Therefore, under the V1a receptor-deficient condition, production of FFAs and glycerol from TG should be enhanced and β-oxidation promoted. Furthermore, AVP shows antilipolytic action and modulates bile acid turnover via the V1a receptor. Clarification of the regulatory mechanism(s) of AVP-induced lipolysis inhibition may contribute to the development of new therapeutic strategies for obesity-related diseases.

In the case of V1b receptor deficiency, lipid metabolism is changed in a different manner from that seen in V1a receptor deficiency. V1bR-KO mice exhibit impaired insulin secretion, which might enhance insulin sensitivity in peripheral tissues as a compensatory mechanism (163, 389, 484) (see the sect. III*F*). When the amount of fat deposit was examined, the ratios of epididymal WAT mass to body weight in V1bR-KO mice were significantly higher than those in control mice at 4, 8, and 10 wk of age (220). In an analysis of isoproterenol-stimulated lipolysis, glycerol production by β-adrenergic receptor stimulation was significantly decreased in differentiated adipocytes obtained from the V1bR-KO mice. In addition, while free carnitine levels in serum were similar between the control and the V1bR-KO mice under fasting conditions, the total acylcarnitine level in serum was lower in the V1bR-KO mice (220). These results for V1bR-KO mice may indicate that β-oxidation is suppressed in V1bR-KO mice compared with control mice. The serum glucose level is known to have a major impact on the serum acylcarnitine level (412, 538). Therefore, enhanced glucose tolerance and higher insulin sensitivity in V1bR-KO mice may contribute to lower serum acylcarnitine in V1bR-KO mice. Since the serum level of leptin, which stimulates lipolysis in adipocytes (458) and inhibits lipogenesis (37, 527), was decreased and adiponectin, which promotes insulin sensitivity (280), was increased in V1bR-KO mice, it is thought that these altered serum levels of adipokines may contribute to the development of altered insulin sensitivity and lipogenesis (220). With these findings taken together, it appears that the AVP/V1b receptor signal regulates insulin sensitivity and adipokine production, and blockade of the AVP/V1b receptor leads to accumulated fat tissue due to suppressed lipolysis and enhanced lipogenesis. Thus AVP is believed to regulate lipid and glucose homeostasis not only through the V1a receptor but also through the V1b receptors.

As described above, AVP exerts contrasting effects on the insulin signal via the V1a and V1b receptors, and altered insulin signals affect the lipid and glucose metabolism by influencing insulin sensitivity. Therefore, we attempted to examine the insulin sensitivity in mice lacking both V1a and V1b receptors (V1abR-KO). V1abR-KO mice had a decreased insulin sensitivity and greater adiposity in total WAT (360). Similar to the finding for V1aR-KO mice, the phosphorylation of Akt in V1abR-KO was decreased compared with that in WT mice (360), indicating that the insulin signal is suppressed in the adipocytes of V1abR-KO mice. These results suggest that the impaired insulin signal caused by V1a receptor deficiency cannot be overcome by the effects of enhanced insulin sensitivity due to V1b receptor deficiency.

F. Glucose Homeostasis

Extracts of neurohypophysis and AVP are known to increase the blood glucose level by directly enhancing glycogenolysis in the liver (44, 91) and by promoting the release of glucagon (129, 543). On the other hand, AVP causes insulin release from pancreatic islets (262), which partially counteracts the effect of the AVP-induced rise in blood glucose. The AVP-induced hepatic glycogenolysis is mediated predominantly by the V1a receptor (250, 348), and the AVP-stimulated insulin release from β cells or glucagon release from α cells of the pancreas is mediated by the V1b receptor (371, 389, 419, 483). A further study with V1bR-KO mice and antagonists for the V1b or OT receptors indicated that the OT receptor is likely involved in the AVP-stimulated glucagon release (164). Although AVP is well recognized as an antidiuretic and vasoconstrictive hormone, these accumulating results suggest that this hormone plays a variety of roles in regulating blood glucose concentration. In this section, we summarize our current knowledge of these AVP-mediated regulations of glucose homeostasis mainly through V1a and V1b receptors.

1. V1a receptor and glucose homeostasis

AVP action on glycogenolysis is mediated via calcium-mobilizing V1a receptors in the liver, and phosphorylase kinase is activated by the Ca^{2+} sensor calmodulin (273). Glucose homeostasis and V1a function have been analyzed in

disease states, such as diabetes mellitus (DM) and impaired glucose tolerance. Increased plasma AVP levels and decreased binding activity of AVP to the liver, where the V1a receptors are predominantly expressed, have been observed in DM subjects or animal models (33, 245, 525). When blood glucose homeostasis of V1a-KO mice was analyzed, plasma glucose levels during a glucose tolerance test (GTT) were significantly higher in V1aR-KO mice, and the glucose infusion rate in a hyperinsulinemic-euglycemic clamp study was decreased in V1aR-KO mice compared with that in WT mice, indicating impaired glucose tolerance (26). If the results obtained from the GTT study are applied to the classification of human DM presently proposed by the American Diabetes Association using the data of plasma glucose levels at 0 and 2 h during the GTT (333), the phenotype of V1aR-KO mice can be classified as pre-DM (26). When treating V1aR-KO mice with a high-fat diet for 15 wk, V1aR-KO mice showed obesity along with hyperleptinemia, adipocyte hypertrophy, and impaired glucose tolerance, which attained the level of DM according to the American Diabetes Association's classification (26). Thus the phenotype of V1aR-KO mice corresponds to the clinical condition of non-insulin-dependent diabetes mellitus (NIDDM) patients (523). Taking into account the phenotype of V1aR-KO mice, Enhörning et al. (144) studied the association between genetic variations in the V1a receptor gene (AVPR1A) and impaired glucose homeostasis in humans, and found that a common genetic variation of the human AVPR1A gene (T allele of rs1042615) is associated with slightly higher fasting glucose and lower triglyceride concentrations in a large population-based sample. Although rs1042615 represents synonymous mutation, the finding regarding the rs1042615 polymorphism in humans is in accordance with the phenotype of V1aR-KO mice.

AVP is well known to stimulate hepatic glycogen degradation through the V1a receptor (272). Therefore, we expected that glycogen levels would be elevated in V1aR-KO mice. However, the rate of hepatic glucose production in our hyperinsulinemic-euglycemic clamp study was increased, and the glycogen content in the livers of V1aR-KO mice was decreased (26). Since the AVP/V1a receptor pathway of glycogen degradation in the liver is abolished in V1aR-KO mice, other mechanisms may be involved in regulating hepatic glucose production in V1aR-KO mice.

In regard to the causal mechanisms of glucose intolerance produced by deleting the V1a receptor gene, we proposed two possible mechanisms: *1*) decreased activity of the central AVP/V1a receptor signal in the CNS and *2*) impaired insulin signaling in peripheral insulin-sensitive tissues (26). With regard to the first possible mechanism, the central AVP/V1a receptor signal in the CNS regulates hepatic glucose production. AVP administration into the NTS or cisterna magna induced hyperglycemia (347, 464, 542). It has also been reported that AVP stimulates GABAergic neurons in vitro (214) and that GABAergic neurons suppress hepatic glucose production (259). Thus central blockade of the V1a receptor may attenuate the stimulation of GABAergic neurons, resulting in the upregulation of hepatic glucose production and decreased hepatic glycogen content (26). Regarding the second possible mechanism, AVP can enhance the insulin-signaling pathway through the V1a receptor. The V1a receptors are expressed in fat, which is an insulin-sensitive tissue (26). Because the phosphorylation of Akt in response to insulin stimulation was significantly reduced in the adipocytes of V1aR-KO mice (218), altered insulin signal in the fat may affect the development of a phenotype with glucose intolerance. Thus the altered insulin signaling pathway produced by a deficient AVP/V1a receptor signal may result in reduced glucose uptake in fat, leading to insulin resistance and altered glucose tolerance.

2. V1b receptor and glucose homeostasis

AVP is a regulator of islet function (535). Marked stimulation of glucagon release and modest stimulation of insulin release were observed during in situ perfusion of the rat pancreas with AVP or OT (130). Stimulation of AVP receptors in pancreatic islet cells led to stimulation of PLC, resulting in the formation of inositol 1,4,5-trisphosphate and diacylglycerol (169). Whereas glucose stimulates an increase in the intracellular Ca^{2+} concentration in pancreatic β cells and causes insulin secretion, AVP can work as a positive modulator for glucose-stimulated insulin release (2, 169). In fact, AVP was ineffective when the concentration of glucose was less than 7 mM, but was very effective with a 30 mM concentration of glucose (169). Studies have been performed to determine the AVP receptor subtype that is responsible for insulin secretion (293, 420). The application of a V1b receptor agonist desamino[D-3-(3′-pyridyl)-Ala^2, Arg^8]VP was reported to increase insulin release from hamster β cells (421). Also, receptor blockade by a mixed V1a/b antagonist, but not by a V1a antagonist, reduced AVP-stimulated insulin release (293, 420). Isolated mouse pancreatic islets express the V1b and OT receptors, but not the V1a or V2 receptor, and AVP-induced insulin release was inhibited by the V1b receptor antagonist SSR149415 but not by the V1a receptor antagonists SR49059 or OPC-21268 (389). Furthermore, the AVP effect on insulin release was entirely lost in mice lacking the V1b receptor (389). A subthreshold dose of AVP that alone did not stimulate insulin secretion was found to potentiate CRH-induced insulin secretion from isolated mouse islets (380). The enhancement of CRH-induced insulin secretion by AVP was not observed in V1bR-KO mice (380). These studies show that the V1b receptor subtype is fully operative in mouse pancreatic islet β cells and that AVP-mediated insulin release appears to be solely via the V1b receptor. How activation of the V1b receptor leads to an increase in insulin secretion is not entirely clear. Upon stimulation of the β cells by AVP, intervals between rhythmic plasma membrane depolarization were significantly shortened, suggesting that a contin-

uously depolarizing current may be generated by AVP (169). Compared with large $[Ca^{2+}]_i$ spikes by AVP at 1.67 mM glucose, 100 nM AVP triggered a transient smaller spike in $[Ca^{2+}]_i$ in the absence of glucose in insulin-secreting HIT cells. Furthermore, in the absence of glucose, AVP did not stimulate membrane depolarization, Ca^{2+} influx, or insulin secretion (316). However, the increase in inositol 1,4,5-trisphosphate was similar at 0 and 1.67 mM glucose levels (316). Also, AVP was previously reported to facilitate the closure of the ATP-sensitive potassium channel, a critical regulator of the plasma membrane potential (97, 324). These results suggest that AVP may regulate calcium and potassium current in a glucose-dependent manner in the β cells.

Acting on α cells in the islets, AVP induces glucagon release (130). A study with V1bR-KO mice showed that the OT receptors, as well as V1b receptors, could mediate AVP-induced glucagon secretion by mouse pancreatic islets (164). In WT islets, AVP-induced glucagon secretion was partially inhibited by the V1b receptor antagonist SSR149415 and further inhibited by cotreatment with both the V1b receptor antagonist and the OT receptor antagonist CL-14–26, whereas a single application of the OT receptor antagonist did not significantly inhibit AVP-induced glucagon secretion. This indicates that the V1b receptors are more active in mediating AVP-induced glucagon secretion than the OT receptors. On the other hand, AVP induced glucagon secretion with the same efficacy in V1bR-KO islets as in WT islets, and the AVP-induced glucagon secretion in V1bR-KO islets was almost completely inhibited by the OT receptor antagonist, suggesting that the OT receptors predominantly mediate AVP-induced glucagon secretion in V1bR-KO mice (164). These findings point to the mutual regulation of AVP- and OT-induced glucagon secretion through the V1b and OT receptors.

Since the V1b receptor is involved in regulating AVP-induced insulin and glucagon secretion in vitro, the effect of V1b receptor deficiency on glucose metabolism was evaluated in vivo in V1bR-KO mice. The fasting plasma levels of insulin, glucagon, and blood glucose were decreased in V1bR-KO mice (163). These findings indicate that blockade of the AVP/V1b receptor signaling may affect glucose homeostasis in vivo. In addition, insulin sensitivity in the peripheral tissues, assessed by the GTT, the insulin tolerance test (ITT), and a hyperinsulinemic-euglycemic clamp study, was significantly enhanced in V1bR-KO mice (163). The V1b receptor is expressed not only in pancreatic islets but also in WAT, which is an insulin-sensitive tissue (163, 220). Further study with cultured adipocytes from WAT revealed that Akt phosphorylation by insulin stimulation was enhanced in V1bR-KO mice compared with that in WT mice, suggesting enhanced insulin signaling in V1bR-KO mice (163). Therefore, hypersensitivity in adipose tissue to insulin and reduced glucagon secretion in the V1bR-KO mice may have contributed to lower levels of plasma glucose, particularly under the fasting condition. Furthermore, glucocorticoid hormones may have affected glucose homeostasis in V1bR-KO mice, because plasma corticosterone levels are lower in some stress conditions in V1bR-KO mice than in WT mice (**TABLES 3** and **4**). In rodents, corticosterone is known to be a key hormone that induces gluconeogenesis in the liver and increases plasma glucose levels (460). Several studies have shown that plasma glucose levels are decreased in adrenalectomized animals or patients with chronic adrenal insufficiency (Addison's disease) (315). Thus, at least in part, decreased corticosterone levels may lead to lower plasma glucose levels in V1bR-KO mice, although the reduction in the basal corticosterone levels is somewhat small in V1bR-KO mice. The reduced plasma glucose levels observed in V1bR-KO mice may have been due to enhanced insulin sensitivity, reduced glucagon, and/or reduced corticosterone levels. Thus glucose metabolism and insulin sensitivity may be modulated by the AVP/V1b receptor system, which plays a crucial role in regulating glucose homeostasis by affecting insulin and glucagon secretion.

3. Glucose homeostasis of V1a and V1b receptor double-KO mice and Brattleboro rats genetically deficient for AVP

AVP plays different roles in regulating glucose homeostasis via the V1a and V1b receptors; AVP may enhance insulin sensitivity via the V1a receptor and suppress sensitivity via the V1b receptor, although the details of AVP's action on glucose homeostasis through each receptor have not yet been fully clarified. To investigate the effect of both V1a and V1b receptor deficiency, V1a and V1b receptor double-deficient V1abR-KO mice were generated and evaluated for glucose tolerance in vivo (360). The GTT revealed that glucose and insulin levels were higher in V1abR-KO mice, which is similar to the phenotype of V1aR-KO, but not to V1bR-KO mice, indicating that deficiency of both receptors resulted in the impaired glucose tolerance. This glucose intolerance in V1abR-KO mice was more pronounced after loading a high-fat diet, as seen in V1aR-KO mice. These findings indicate that the effects of V1b receptor deficiency may not influence the development of glucose intolerance promoted by V1a receptor deficiency, and that blockade of both receptors may lead to impaired glucose tolerance (360).

On the basis of these findings in the KO mouse models (V1aR-KO, V1bR-KO, and V1abR-KO), Brattleboro rats, which genetically lack AVP, would be expected to be display a glucose-intolerant phenotype, similar to that of V1abR-KO mice. However, Brattleboro rats showed enhanced glucose tolerance (362). This obviously brings into question the potential role of the V2 receptor in glucose homeostasis. There is evidence that the V2 receptor is expressed in the heart, liver, WAT, BAT, and muscle tissues

(163), all of which are insulin-sensitive tissues. Whether the extrarenal V2 receptor is expressed as an intact receptor protein and plays a role in glucose metabolism needs to be addressed. Additionally, OT signals may also be involved in the altered glucose tolerance of Brattleboro rats. Brattleboro rats have an increased level of plasma OT, which acts to regulate glucose tolerance as well as energy homeostasis (84, 481). Furthermore, it has also been reported that, in addition to the plasma OT level, the expression of the OT receptor is elevated in Brattleboro rats (57, 361), suggesting that OT signals are promoted in Brattleboro rats, and may contribute to the enhanced glucose tolerance.

These findings on the glucose tolerance in mutant animals are summarized in **TABLE 5**. Although the details of AVP actions on glucose homeostasis through the V1a, V1b, V2, and OT receptors have not yet been fully clarified, these studies have contributed significantly to the understanding of the important roles played by AVP and the V1a/V1b receptors in glucose tolerance.

G. Immune Functions

AVP and OT are present not only in the neuroendocrine system but also in immune tissues such as the thymus in humans and rats, although OT is a dominant peptide in the thymus (171, 345). Certain subtypes of thymic epithelial cells, the medullary epithelium, the cortical surface epithelium, and some intracortical epithelial cells show strong immunohistochemical reactivity with antisera against OT, AVP, and neurophysin (345). These epithelial cells also show positive immunoreactivity with anti-cytokeratin AE1/E3 antibodies. This restricted expression suggests a tightly controlled microenvironment for T-cell development. OT and AVP are also expressed in murine spleen eosinophil-like cells (281). Concerning the receptors for AVP and OT expressed in the immune tissues, OT binding sites have been detected in the rat thymus and thymocytes (137), and V1 AVP receptors have been detected in rat splenic membrane preparations and splenic lymphocytes (136). To determine the importance of the V1a receptor in the development and function of the immune system, receptor KO mice were generated and investigated (228). In the mutant mice lacking the V1a receptor, the B-cell populations in the spleen and lymph node are shifted towards the mature $IgM^{low}IgD^{high}$ phenotype compared with WT mice. Moreover, a subset of B cells, the CD5 and Mac-1-expressing B-1a B cells, are increased in V1aR-KO mice. These changes indicate that the V1a receptor may downregulate B-cell activation (228). Accordingly, B cells from V1aR-KO mice strongly responded to and proliferated in response to anti-IgM stimulation. In addition, the basal serum levels of the IgG2a class antibodies in V1aR-KO mice were significantly increased. Thus the V1a receptor appears to play a role in regulating both B-1 and B-2 cell development (228), although its contribution to a plethora of factors that act as immune modulators is presently unknown.

Table 5. *Glucose homeostasis of mutant animal models*

	NC diet							HF diet						
	Basal			GTT		ITT	Clamp	Basal			GTT		ITT	
	glucose	insulin	glucagon	glucose	insulin	glucose	GIR	glucose	insulin	glucagon	glucose	insulin	glucose	References
V1aR-KO	Increase	No difference	ND	Increase	No difference	ND	Decrease	increase	no difference	ND	increase	ND	ND	26
V1bR-KO	Decrease	Decrease	Decrease	Decrease	Decrease	Decrease	Increase	decrease	decrease	ND	decrease	decrease	ND	163, 360
V1abR-KO	No difference	Increase	ND	Increase	Increase	Increase	ND	no difference	increase	ND	increase	increase	increase	360
BB rat	No difference	Decrease	ND	Decrease	Decrease	ND	ND	ND	ND	ND	ND	ND	ND	362

ND, not determined. Significant differences from WT control are indicated.

IV. V1a AND V1b RECEPTORS IN THE CENTRAL NERVOUS SYSTEM

AVP works not only as a peripheral hormone but also as a neuropeptide that is capable of influencing a wide variety of brain functions such as social behavior, emotionality, learning and memory, and thermoregulation (111, 160). Studies on species-specific localization of central AVP receptors and genetic manipulation of the receptor expression in model animals have greatly advanced our understanding on the behavioral effects of AVP. In this section, we summarize and discuss recent findings obtained mainly by studies on mice lacking V1a or V1b receptors.

In the CNS, parvocellular AVP neurons of the PVN, bed nucleus of the stria terminalis (BNST), medial amygdala (MeA), and suprachiasmatic nucleus (SCN) project to a variety of brain and spinal regions (78, 179). A comprehensive report on the distribution of the AVP neurons and fibers in the CNS of C57BL/6 mice was recently published (428). The distributions of AVP receptor subtypes in the CNS show significant species difference (510). The abundantly expressed receptors for AVP in the brain are the V1a and OT receptor subtypes (255, 511); no V2 receptor-specific ligand binding or V2 receptor mRNA has been reported (41, 157), with the exception of an autoregulatory V2 receptor in the AVP neurons (440). The V1b receptor in the mouse CNS is found most prominently in the hippocampus, but is also found in the cerebral cortex, amygdala, olfactory bulb, and hypothalamus, including the PVN (547). This AVP and its corresponding receptor systems are the basis of the behavioral phenotype observed in the receptor KO mice. For a detailed description of each topic in this section and information on the relationship between the AVP receptor and the OT receptor system, previous reviews should also be consulted (82, 128, 238, 336, 408). Recent studies investigating the behavioral roles of AVP using receptor antagonists and mutant animals (KO mice and Brattleboro rats) are summarized in **TABLE 6**.

A. Social Behavior

1. Pair-bonding behavior

AVP is critical for the expression of a variety of social behaviors in many species. Young et al. (544) reported that centrally administered AVP increases affiliative behavior (partner preference) in the highly social and monogamous prairie vole, but not in the relatively asocial promiscuous Montane vole. The expression pattern of the V1a receptor gene in the brain is functionally associated with species-typical monogamous behaviors: the high intensity of V1a receptor-specific binding in the lateral septum (LS) of the Montane vole but not the prairie vole, and in the diagonal band (DB) of the prairie vole but not the Montane vole (239, 544). Partner preference is also increased by bilateral infusion into the ventral pallidum (VP) of the adeno-associated viral vector containing the prairie vole V1a receptor gene in male meadow voles (305). Furthermore, intracerebroventricular injection of mixed V1a/OT receptor antagonist disrupted both the formation and expression of partner preference in male prairie voles (127). Although prairie voles are considered socially monogamous, in natural settings, some males do not cohabit with one female. Such males become nonterritorial "wandering" males, which have expanded home ranges that overlap with many males and females. When individual variations in male behavior and expression patterns of the V1a receptor were examined, social fidelity measured by space use and sexual fidelity measured by mating success were associated with V1a receptor expression in the posterior cingulate/retrosplenial cortex (PCing) and dorsal thalamus (laterodorsal nuclei, LDThal), but not the VP or the LS, of male prairie voles in semi-natural settings (387) **(FIGURE 7)**. In humans, there is an association between one of the V1a receptor genotypes and traits reflecting pair-bonding behavior in men, including partner bonding, perceived marital problems, and marital status (526). Thus the V1a receptor is strongly implicated in pair-bonding behavior in the males of several species.

2. Parental behavior

AVP has been implicated in the central mediation of parental behavior. Brain AVP has been shown to be an important regulator of female social behavior, including maternal care and maternal aggression in lactating rats (59, 60). Furthermore, AVP release significantly increases in the medial preoptic area (MPOA) or tends to increase in the BNST during different phases of maternal care (61). Though V1aR-KO mice display normal maternal aggression (532), blocking the V1a receptor by intracerebroventricular infusion of a selective V1a receptor antagonist or local administration of V1a antisense oligonucleotide into the MPOA impairs maternal care (59, 370). Moreover, chronic infusion of the V1a receptor antagonist into the MeA impairs maternal memory (369). In contrast, local injection of the V1a receptor antagonist bilaterally into the BNST reduces maternal aggression but not maternal care (61). Thus the brain AVP system together with the V1a receptor can modulate maternal behaviors (see **TABLE 6** and **FIGURE 7**).

In non-human primates, male marmosets display paternal behavior and the prefrontal cortex of marmoset fathers show enhanced density of dendritic spines and increased expression of the V1a receptor in the spines (279), suggesting that V1a receptors play a role in paternal care.

3. Social interaction and social communication

Social interactions affect every aspect of our lives. Autism spectrum disorders (autism, Asperger's syndrome, and high-functioning autism) are characterized by a common pattern of

Table 6. *Effects of V1a and V1b receptor antagonists,and gene knockout on psychological and cognitive behaviors*

Behavioral Classes	Intervention	Animal Species	Changes	Reference Nos.
		Social behavior		
Partner preference	AVP i.c.v.	Social prairie vole	↑	544
	Transgenic of prairie vole V1a	Mouse	↑	544
	V1a gene transfer to VP	Asocial meadow vole	↑	305
	V1a antagonist i.c.v.	Male prairie vole	↓	127
Maternal behavior	V1a antagonist i.c.v.	Rat	↓	59
	Chronic central AVP	Rat	↑	59
	V1a gene transfer to MPOA	Rat	↑	59
	V1a antisense to MPOA	Rat	↓	59
	V1a KO	Mouse	–	532
Maternal memory	V1a antagonist into MeA	Rat	↓	369
Maternal aggression	V1a antagonist into BNST	Rat	↓	61
Social interaction	V1a KO	Mouse	↓	135
	V1b KO	Mouse	↓	132
		Learning and memory		
Social recognition	Genetic deficit of AVP	BB rat	↓	141, 147
	AVP to septum	BB rat, LE rat	↑	141
	V1a antagonist to septum or OB	Rat	↓	48, 141, 503
	Small interference RNA against V1a to OB	Rat	↓	503
	Ablation of AVP neurons in OB	Rat	↓	503
	V1a gene to LS	Rat	↑	48, 287
	V1a KO	Mouse	↓ or –	49, 532
	V1b KO	Mouse	↓	119, 533
Spatial learning	V1a antagonist in radial arm maze	Mouse	↓	134
	V1a KO in radial arm maze	Mouse	↓	134
	V1b KO in radial arm maze	Mouse	–	134
	V1a KO in Morris water maze	Mouse	–	49, 134
	V1b KO in Morris water maze	Mouse	–	533
		Aggression		
	AVP to AH	Male hamster	↑	81, 154
	V1a/Ox antagonist to AH	Male hamster	↓	155
	V1a/Ox antagonist to AH	Female hamster	↑	197
	AVP to VLH	Male hamster	↑	116
	Oral V1a or V1b antagonist	Male hamster	↓	55, 153
	V1a KO	Mouse	–	532
	V1b KO	Mouse	↓	531, 533
		Anxiety		
	V1a or V1b antagonist	Rat, mouse and guinea pig	↓	56, 186, 223
	V1a antagonist to VH	Rat	↓	142
	V1b antagonist to DH	Rat	↓	142
	V1b antagonist to BLA	Rat	↓	436
	V1a gene to LS	Mouse	↑	48
	V1a KO	Mouse	↓ or –	49, 135, 532
	V1b KO	Mouse	–	133, 533
		Depression		
	V1b antagonist to BLA, CeA, MeA, LS	Rat	↓	436, 467
	V1a KO	Mouse	–	49, 135, 532
	V1b KO	Mouse	–	133, 533

Table 6.—*Continued*

Behavioral Classes	Intervention	Animal Species	Changes	Reference Nos.
		Prepulse inhibition		
	Genetic deficit of AVP	BB rat	↓	146, 148
	V1a KO	Mouse	↓ or –	49, 132
	V1b KO	Mouse	↓	133
		Water intake		
	V1b KO	Mouse	↑	105
		Food intake		
	V1a KO	Mouse	↓	26, 28
		Alcohol intake (and preference)		
	V1a KO	Mouse	↑ or –	83, 437
	V1b KO	Mouse	–	83
	V1b antagonist	Rat	↓	553
		Circadian rhythm		
	V1a KO	mouse	↓	(532)

The involvement of V1a and V1b receptors in psychological and cognitive behaviors is indicated as follows: ↑, increase or improvement; ↓, decrease or reduced; –, no change; LE rat, Long-Evans rat used as control for BB rat.

marked impairments in social interactions (86). Some studies have suggested that polymorphisms of the V1a receptor gene are associated with autism spectrum disorders (242, 268). Furthermore, the amygdala reactivity in a functional magnetic resonance imaging study was found to be associated with genetic variations in the promoter of the V1a receptor gene, which are linked to autism, and may therefore represent a neural mechanism that mediates the genetic risk for autism spectrum disorders (337).

Impairments of social function are often observed as symptoms of schizophrenia. Phencyclidine (PCP), a hallucinogenic NMDA receptor antagonist, is known to induce symptoms of schizophrenia and increase its severity in healthy individuals (359, 512). Subchronic treatment of rats with PCP resulted in impaired social interactions and reduced density of the V1a receptor in the BNST, LS, substantia nigra (SN), lateral hypothalamic area (LH), and other regions (482). Moreover, NC-1900, an AVP(4–9) peptide analog, ameliorated social interaction deficits induced by MK-801, an NMDA receptor antagonist (325). It is possible that the central AVP plays an important role in the regulation of social interaction. This is of special interest because impaired social interaction is among the core deficits of autistic disorders.

V1aR-KO and V1bR-KO mice were shown to exhibit impaired social interaction compared with WT mice (132, 135). In addition, V1bR-KO mice exhibited reduced social motivation in an olfactory discrimination task, but normal motivation after food deprivation, indicating that the deficit in motivated behavior is not general (533). Therefore, the reduced social motivation may be linked to the impairment of social interaction in V1bR-KO mice.

Interestingly, intranasal delivery of AVP has been reported to affect social communication processes in humans (500). In men, AVP stimulates agonistic facial motor patterns in response to the faces of unfamiliar men and decreases perceptions of the friendliness of those faces. In contrast, in women, AVP stimulates affiliative facial motor patterns in response to the faces of unfamiliar women and increases perceptions of the friendliness of those faces. AVP also affects autonomic responsiveness to threatening faces and increased anxiety. Since intranasal administration of AVP has been reported to elevate its concentration in the cerebrospinal fluid (CSF) within 30 min in healthy humans (58), these results suggest that AVP in the CNS modulates social and emotional behavior in humans.

B. Learning and Memory

The role of AVP in memory was one of the first functions of central AVP that have been characterized, and social memory and social cognition in particular have been extensively examined (180, 332). Social recognition is a unique form of learning and memory that involves the process of the recognition of individuals by utilizing a neural mechanism that is specific for social processing. Social recognition tests make use of the animals' natural tendency towards the olfactory investigation of unfamiliar conspecifics. When a subject animal is exposed to unfamiliar conspecific juveniles at least two times before and

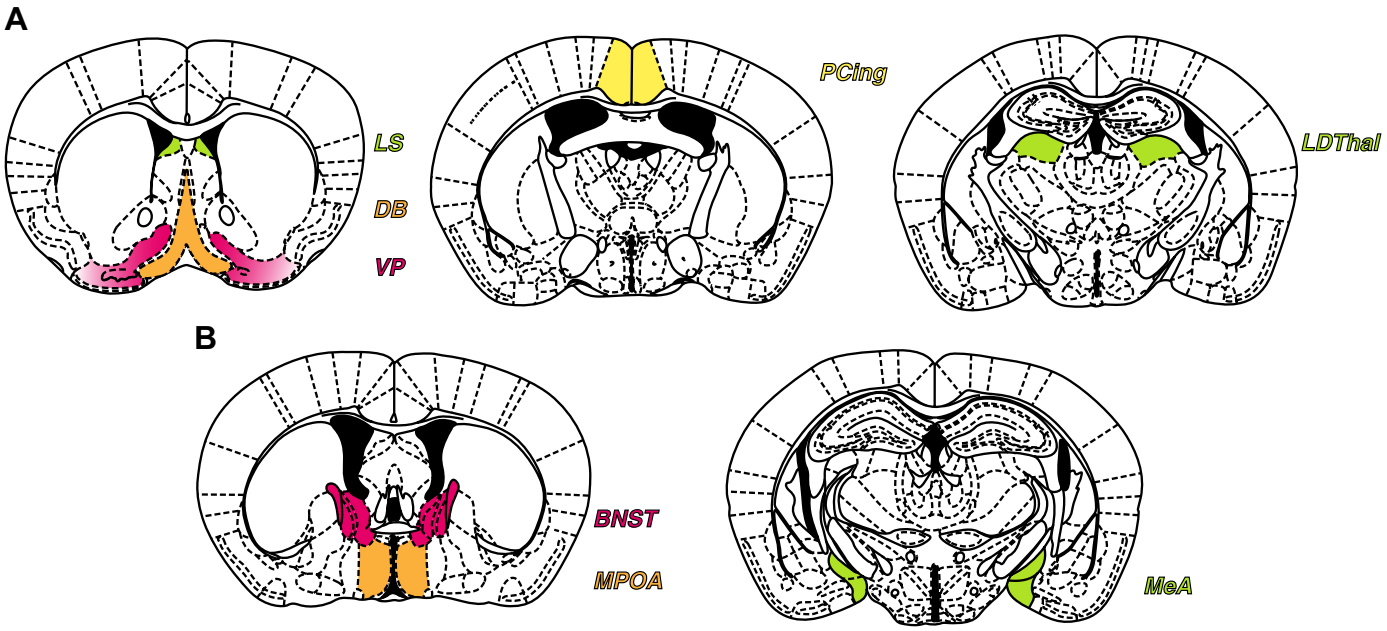


FIGURE 7. Brain structures associated with the AVP-induced pair-bonding and parental behaviors. The expression patterns of the V1a receptor in the brain are functionally associated with pair-bonding (*A*) and parental (*B*) behaviors. The findings from such studies using different rodent species are plotted on the corresponding brain structures of mouse. *A*: the V1a receptor-specific binding is increased in the lateral septum (LS) of the promiscuous Montane vole and in the diagonal band (DB) of the monogamous prairie vole. Partner preference is also increased by overexpression of the V1a receptor in the ventral pallidum (VP). V1a expression in posterior cingulate/retrosplenial cortex (PCing) and laterodorsal thalamic nuclei (LDThal) is reduced in the nonterritorial prairie vole. *B*: during maternal care, AVP release is increased in the medial preoptic area (MPOA) or in the bed nucleus of the stria terminalis (BNST). Chronic infusion of the V1a receptor antagonist into the medial amygdala (MeA) impairs maternal memory, whereas injection of the V1a receptor antagonist into the BNST reduces maternal aggression. Distributions of brain areas expressing V1a receptors were plotted on to templates modified from the mouse brain atlas of Paxinos and Franklin (396). [From Paxinos and Franklin (396), copyright 2007 Elsevier.]

after a fixed interval, at the second exposure, the subject animal recognizes the previously exposed conspecific and the investigation duration is shortened (106).

When Brattleboro rats were examined, they displayed a deficit in social recognition that was improved by microdialysis administration of synthetic AVP into the LS (141, 147), providing strong evidence for the physiological role of AVP in social recognition. In normal rats, bilateral application of an adeno-associated viral vector containing the prairie vole V1a receptor gene into the LS resulted in a stable increase in V1a receptor binding density, and an improvement of social recognition and active social interaction (287). This facilitation of social recognition is blocked by microdialysis administration of a selective V1a receptor antagonist. The critical role of the V1a receptor in social recognition has also been demonstrated in male V1aR-KO mice that exhibit a profound impairment in social recognition (49). Furthermore, it was demonstrated that the LS, but not the MeA, is critical for social recognition using site-specific injections of a selective V1a receptor antagonist (48). Re-expressing the V1a receptor in the LS of V1aR-KO mice using a viral vector resulted in a complete restoration of social recognition capability. Moreover, overexpression of the V1a receptor in the LS of WT mice resulted in a potentiation of social recognition behavior. Thus the V1a receptor in the LS plays a critical role in the neural processing of social stimuli required for complex social behavior. Indeed, the LS contains a high density of V1a receptors (511). Unexpectedly, however, Wersinger et al. (532) reported that social recognition was unaffected in V1aR-KO mice. Whether this discrepancy is due to slightly different strain backgrounds or testing procedures is unknown, but it is clear from previous work that the V1a receptor in the LS is important for social recognition.

V1bR-KO mice also showed a mild deficit in social recognition and memory for temporal order (119, 533). V1bR-KO mice could recognize previously explored objects and remember where they were experienced, but their ability to remember the temporal order of the presentation of those objects was impaired (119). V1bR-KO mice were also impaired in an object-odor paired associate task that involved a temporal discontinuity between the associated elements (119). However, V1bR-KO mice are able to learn a set of overlapping odor discriminations and can infer relationships among odors that were only indirectly associated (i.e., transitive inference), indicating intact relational memory (119). The V1b receptor is expressed in the pyramidal cells of the hippocampal CA2 area at much higher levels than

in any other part of the brain (547). Therefore, the V1b receptor, perhaps in CA2, is thought to play a highly specific role in social behavior and episodic memory (119).

The rat olfactory bulb (OB) contains a large population of interneurons, which express AVP (503). Infusion of a small interference RNA (siRNA) targeted against V1a receptor mRNA or administration of the V1a receptor antagonist OPC-21268 bilaterally into the OB impaired the social recognition abilities of rats (503). In male prairie voles, the V1a receptor binding in the OB and social behaviors (paternal care, juvenile affiliation, partner preference, and resident intruder reactivity) were correlated, and partner preference behavior showed high correlation with V1a receptor binding in the OB, VP, amygdala [including the central amygdala (CeA) and the MeA], and other brain areas (198). Although V1aR-KO mice did not display a general deficit in olfactory habituation in a study that used scented cotton balls (49), the same V1aR-KO line showed subtle olfactory deficits in habituation and dishabituation to urine and to almond odors, as well as to hidden cookies (532). These findings indicate that social information is processed in part by AVP via V1a receptor activation in the olfactory system.

AVP has been shown to directly interact with other neurotransmitter systems in the olfactory system. In particular, the NE system appears to be critical to AVP-mediated social memory. Depletion of NE using 6-hydroxydopamine (6-OHDA) in the OB of male rats abolished AVP facilitation of social recognition but did not block normal social recognition (125). These findings suggest that AVP may affect social recognition by activating the NE system.

In an examination of spatial learning, V1aR-KO mice, but not V1bR-KO mice, exhibited impairment in a radial arm maze (134). However, V1aR-KO and V1bR-KO mice performed normally in a Morris water maze (49, 132, 134, 533). Thus it appears that the V1a receptor is required for working memory or a high level of spatial memory in a radial arm maze.

C. Aggression, Anxiety, and Depression

1. Aggression

Aggressive behavior was increased when AVP was microinjected into the anterior hypothalamus (AH) in male Syrian hamsters using a resident-intruder paradigm (81, 154) and inhibited when a V1a/OT receptor antagonist was microinjected into the AH (155). Furthermore, it was found that social isolation increases aggression by increasing the number of V1a receptors in the AH in male Syrian hamsters (13). Conversely, aggression is increased by injection of the selective V1a/OT receptor antagonist into the AH in female Syrian hamsters (197). These data suggest that AVP-sensitive neurons in the AH are involved in the control of aggression in male and female hamsters.

The selective V1a receptor antagonist SRX251 was found to reduce offensive aggression toward intruders in male hamsters (153). Similarly, the V1b receptor antagonist SSR149415 was found to reduce offensive aggression (55). The V1b receptor appears to be critical to the proper expression of aggression, as V1bR-KO mice show reduced aggression (531, 533). Wersinger et al. (532) reported that social aggression was unaffected in V1aR-KO mice. This may be due to developmental compensation and is not thought to reflect the pharmacologically identified role of the V1a receptor in the modulation of aggression.

2. Anxiety and depression

Elevated AVP levels are associated with several anxiety disorders. AVP concentrations in both the CSF and plasma are elevated in patients with obsessive-compulsive disorder (OCD) (20). AVP concentration and the ratio of AVP to OT are negatively correlated with the severity of several OCD symptoms in children with OCD (475). In panic disorder patients, polymorphisms in the V1b receptor and the CRH-R1 genes alter the susceptibility to panic disorder (265). Clinical studies have also demonstrated the involvement of AVP in depressive disorders. Plasma levels of AVP (517, 518), the number of AVP-expressing cells or the levels of AVP in the PVN of the hypothalamus (407), and the response of pituitary AVP (124) are increased in depressed patients. The AVP mRNA in the SON is also increased in depressed subjects (339). In contrast, AVP mRNA expression in the PVN and SON is unchanged in depressed patients with Alzheimer's disease compared with nondepressed patients with Alzheimer's disease (338). Interestingly, two studies found a correlation between plasma AVP levels and cortisol levels in depression, particularly in suicide victims (112, 232), but this finding was contradicted by another report (75). Increased expression of the V1a receptor gene was found in the PVN of depressed patients (529). A single nucleotide polymorphism (SNP) in the V1b receptor gene was also found to be protective against major depression (519). In addition, a genetic association has been reported between polymorphisms in the V1b receptor gene and childhood-onset mood disorders (117). These reports suggest the involvement of the AVP system (in particular, the V1b receptor) in anxiety and depressive disorders (472).

To investigate the role of the V1a and V1b receptors in anxiety and depression, pharmacological and transgenic studies have been performed in rodents. In male prairie voles, V1a receptor binding in thalamic areas and anxiety-related behavior were positively correlated, indicating that animals with higher binding density in the thalamus show more trait anxiety, which is a tendency to react with anxiety (198). This suggests that the V1a receptor plays a role in the thalamus in behaviors with a strong anxiety component. In previous studies, V1aR-KO mice showed reduced anxiety-related behavior in the elevated plus-maze, light/dark, and open-field tests (49, 135). Furthermore, overexpression of

the V1a receptor in the LS of WT mice resulted in an increase in anxiety-related behavior (48), suggesting the involvement of the V1a receptor in regulating anxiety. However, Wersinger et al. (532) reported that the anxiety-like behavior was unaffected in this line. Differences in strain background, testing procedures, and situations may account for this discrepancy. Also, their and our groups reported that V1bR-KO mice show normal anxiety levels in the elevated plus-maze and light/dark tests (133, 533). Moreover, using a marble-burying test, we confirmed that there was no significant difference between V1bR-KO mice and WT mice in the number of marbles buried (132), whereas V1aR-KO mice buried significantly fewer marbles than WT mice did (135). It has been suggested that the burying behavior would be rewarding or compulsive (70). The reduced number of marbles buried by V1aR-KO mice may thus reflect an anti-OCD effect or an anxiolytic effect of the mutation. This idea is supported by the findings that V1aR-KO mice show reduced anxiety-related behavior in various tests.

Bleickardt et al. (56) reported that the V1a receptor antagonist JNJ-17308616 significantly reduced anxiety-like behavior in five models of anxiety: rat elevated plus-maze, rat pup separation-induced ultrasonic vocalizations, mouse marble burying, rat elevated zero-maze, and rat conditioned lick suppression. The V1b receptor antagonist SSR149415 produced anxiolytic-like (in elevated plus-maze, light/dark tests, etc.) and antidepressant-like (in forced swimming and chronic mild stress tests) effects in rodents (186). Hodgson et al. (223) reported that SSR149415 was effective in the anxiety models, such as separation-induced pup vocalizations, elevated plus-maze, and conditioned lick suppression tests, but ineffective in marble burying and two tests for depression (forced swimming and tail suspension). Chronic but not acute administration of SSR149415 also normalized olfactory bulbectomy-induced hyperactivity up to 1 wk after cessation of treatment (68), suggesting that the V1b receptor antagonist may have long-lasting antidepressant activity (19). In addition, the anxiolytic-like effect of acute administration of a SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI) was abolished in both V1bR-KO mice and SSR149415-treated mice. Moreover, the anxiolytic-like effect of chronic administration of an SSRI was abolished in V1bR-KO mice, while that of a SNRI was unchanged in these mice, suggesting that the V1b receptor may be partly involved in the anxiolytic-like action of SSRIs (241). These findings indicate that V1a and V1b receptors play a role in the control of emotional responses.

Salomé et al. (436) reported that in rats, the microinjection of SSR149415 into the basolateral amygdala (BLA), but not into the CeA or the MeA, yielded reduced anxiety-like behavior in the elevated plus-maze test, and that the rats which had received microinjection of the drug into the CeA, BLA, or MeA showed antidepressant-like reactions in the forced swimming test (436). Bilateral intraseptal infusion of SSR149415 produced antidepressant-like effects but not anxiolytic-like effects (467), suggesting that the V1b receptors in the LS participate in the antidepressant- but not the anxiolytic-like action of SSR149415 in rats. Moreover, microinjection of a mixed V1a/OT receptor antagonist, $d(CH_2)_5[Tyr(Me)^2]AVP$, into the VH but not the dorsal hippocampus (DH) reduced anxiety-like behavior, while microinjection of SSR149415 into the DH but not the VH reduced anxiety-like behavior in rats (142). V1a receptor signaling and V1b receptor signaling in the LS, amygdala, and hippocampal areas are critical in the regulation of anxiety- and depression-related behaviors. However, V1aR-KO and V1bR-KO mice performed normally in the forced swimming test (49, 133, 135, 532). Additionally, V1bR-KO mice displayed a normal anxiety-like response in the elevated plus-maze and light/dark tests (133, 533).

Both agreement and disagreement are seen between analyses using V1bR-KO mice and V1b receptor antagonists. In studies on aggressive behaviors, the results were consistent, and interfering with V1b receptor function resulted in reduced aggressive behavior (55, 429, 531, 533). In contrast, no change in anxiety-like or depression-like behaviors was observed in V1bR-KO mice, in spite of the fact that a V1b receptor antagonist had an inhibitory effect on these conditions (429). The discrepancies between transgenic data and pharmacological data may arise from the compensated state of the transgenic mice, in which the V1b receptor is deleted throughout their development. We (484) have reported that V1bR-KO mice have lower circulating ACTH levels under basal and acute stress conditions, while Lolait et al. (313) observed that their V1bR-KO mice maintained normal resting ACTH levels under basal and acute restraint but not chronic restraint, indicating basal HPA axis differences between both V1bR-KO lines. In addition, the results from studies on anxiety and depression in V1bR-KO animals obviously differ from results obtained from studies on Brattleboro rats (343) or rats treated with V1bR antagonists (see above). Roper et al. (429) strongly suggested that the V1bR-KO mouse is not an appropriate model for examining stress-induced anxiety or depression. Therefore, the active application of molecular techniques such as conditioned KO mice and development of new animal paradigms (including new methods of studying anxiety and depression) are needed to elucidate the molecule(s) involved (260).

D. Sensorimotor Gating Function

Transgenic and pharmacological data indicate that the V1b receptor regulates the HPA system and plays a prominent role in stress-related behavior (see the sect. IIIC). Jansen et

al. (249) reported that schizophrenic patients displayed selective impairments in response to psychosocial stress but not physical stress, suggesting that HPA stress responses may be impaired in schizophrenic patients. Several studies have stressed the role of AVP in the psychopathology of schizophrenia (139, 336). In addition, neonatal lesions of the ventral hippocampal formation, which replicate several features of schizophrenia, disrupt neuroendocrine (including AVP) responses to auditory stressors in adult rats (342). Thus AVP may be involved in the course of schizophrenia.

In an attempt to better understand the mechanisms underlying the pathophysiology of schizophrenia, sensorimotor information gating processes have received a great deal of attention (174). One well-established method for evaluating sensory filtering is the paradigm of prepulse inhibition (PPI), which is a reduction of the startle reflex produced by implementation of a low-intensity prepulse immediately before the startle stimulus. The disruption of PPI in schizophrenic patients has been well described in several studies (65, 403).

Brattleboro rats exhibit deficits of PPI of the startle reflex, suggesting that central AVP may play an important role in the regulation of PPI (146, 148). Although it has been reported that V1aR-KO mice show normal PPI of the startle reflex (49), both V1aR-KO and V1bR-KO mice were found to display significantly reduced levels of PPI (132, 133), reminiscent of the sensorimotor gating deficits observed in a large majority of schizophrenic patients. This discrepancy may be due to differences in strain background and/or testing procedures and situations. In addition to PPI deficits, V1aR-KO and V1bR-KO mice show an increased acoustic startle response. However, the acoustic startle response is not significantly correlated to the PPI of the startle reflex in individual V1aR-KO and V1bR-KO mice. These findings indicate that both V1a and V1b receptors are involved in the gating step of the sensorimotor functions. Interestingly, in Brattleboro rats, the individual startle responses and PPI are not correlated, as they are in the KO mice (146, 148). More recently, polymorphisms in the promoter region of the V1a receptor gene have been associated with the PPI response to auditory stimuli in humans (297).

Moreover, PPI deficits observed in V1bR-KO mice were significantly reversed by atypical antipsychotics such as risperidone and clozapine but not by the typical neuroleptic haloperidol, a D_2 receptor antagonist, as seen in schizophrenic patients (133, 282). Thus our results are in good agreement with clinical data obtained on schizophrenic patients. Interestingly, the PPI deficits observed in Brattleboro rats were also reversed by the administration of clozapine but not haloperidol (146). The finding that the PPI deficits in V1bR-KO mice are not reversed by haloperidol indicates that excessive DA transmission per se does not fully explain the pathogenesis of V1bR-KO mice. On the other hand, risperidone and clozapine work not only as D_2 receptor antagonists but also as serotonin 5-HT_{2A} receptor antagonists. Therefore, it is possible that risperidone and clozapine reverse PPI deficits in V1bR-KO mice through a simultaneous blockade of D_2 and 5-HT_{2A} receptors. More importantly, V1bR-KO mice show a decrease in the basal levels of extracellular DA in the medial prefrontal cortex (MPC) compared with WT mice, while extracellular serotonin (5-HT) in the same site is not different between the two genotypes. Therefore, the V1b receptor may regulate DA release in the MPC. The MPC is thought to play an important role in the neuronal circuit response of PPI (476). Also, dopaminergic hypofunction in the prefrontal cortex is related to the etiology of negative symptoms of schizophrenia (107). Furthermore, PPI was reduced by manipulation of dopaminergic hypofunction in the MPC by infusion of 6-OHDA (277) or antagonists to D_1 or D_2 receptors (138). These findings suggest that dopaminergic hypofunction in the MPC may be involved in PPI deficits in V1bR-KO mice.

E. Other CNS Functions

1. *Water intake, food intake (appetite), and alcohol intake (preference)*

The studies with KO mice and/or antagonists reveal that AVP is associated with water intake, food intake (appetite), and alcohol intake (preference). V1bR-KO mice show increased water intake and urine volume, suggesting that AVP may suppress drinking behavior via the V1b receptor in the CNS (105). V1aR-KO mice exhibit decreased daily food intake (26). On the other hand, V1bR-KO mice show food motivation after its deprivation (533). In humans, a microsatellite polymorphism in the V1a receptor promoter region has been reported to be associated with eating behavior (35). Further studies on appetite that employed V1aR-KO mice and V1a receptor antagonists revealed that orexigenic responses to neuropeptide Y (NPY) stimulation are enhanced in V1aR-KO mice and V1a receptor antagonists-treated mice (29). These findings suggest that AVP may suppress NPY-induced orexigenic stimuli via the V1a receptor, and blockade of the AVP/V1a signal may lead to enhancement of the NPY-induced orexigenic effect.

One study found that V1aR-KO mice display increased ethanol consumption and preference (437), but another study found contradictory evidence (83). Also, one study and our unpublished study found that V1bR-KO mice do not show an increase in ethanol consumption and preference (83) (Tanoue et al., unpublished data). It has been suggested that AVP inhibits the release of glutamate from the presynaptic terminal via the V1a receptor. Blockade of AVP/V1a receptor signaling results in elevation of glutamate levels in the CNS, which accordingly leads to increased ethanol consumption and preference (437).

In Sardinian rats, basal AVP mRNA levels in the MeA, CeA, and medial hypothalamus of alcohol-naive alcohol-preferring rats are higher than those in alcohol-nonpreferring rats, and alcohol consumption decreases AVP mRNA levels in these brain regions of alcohol-preferring rats (553). Acute treatment with the V1b receptor antagonist SSR149415 significantly reduced the alcohol intake of alcohol-preferring rats. Thus the stress-responsive AVP/V1b receptor system is one component of the neural circuitry underlying high alcohol consumption in Sardinian alcohol-preferring rats.

2. Circadian rhythm

Intercellular communication between the SCN and its target neurons is critical for the generation of coherent circadian rhythms. At the molecular level, neuropeptides encoded by clock-controlled genes have been identified as important output mediators. AVP is the product of one such clock-controlled gene in the mouse SCN (254). The concentrations of AVP in the CSF vary during the circadian cycle, with morning levels approximately five times higher than those of night hours (418). V1a receptor mRNA levels also display a circadian rhythm in the SCN, peaking during night hours (299). The circadian rhythmicity of locomotor activities is significantly reduced in V1aR-KO mice. However, the light masking and light-induced phase shift effects are intact in V1aR-KO mice. When free-running in constant darkness, V1aR-KO mice have a longer circadian tau than WT mice in the wheel-running activity (532). These studies thus indicate that V1a receptor signaling plays an important role in the generation of overt circadian rhythms.

3. Water homeostasis and thermoregulation

Water homeostasis is critical for survival in land mammals. Mice display increased locomotor activity when dehydrated, a behavior that improves the likelihood of locating new sources of water and simultaneously places additional demands on compromised hydration levels. While intracerebroventricular injection of AVP or water deprivation increased locomotor activity in control WT mice, V1aR-KO mice were found to be less active than WT mice (513). AVP activates orexin neurons via the V1a receptor, leading to increased spontaneous locomotor activity in mice. Thus this AVP/V1a receptor signaling is associated with water deprivation-induced hyperlocomotor activity, a response to dehydration that increases the chance of locating water in nature.

AVP is known to play a role in thermoregulation in the CNS and peripheral tissues. Intravenous injection of LVP caused a decrease in heat production, followed by a fall in colonic temperature by decreasing adipose metabolism, which is at least partly due to suppression of BAT thermogenesis (456). The hypothermic effect of LVP administered peripherally has been largely attributed to the baroreflexive suppression of nonshivering thermogenesis (456). AVP has also been reported to work as an endogenous antipyretic molecule in the CNS (243, 263, 368). The AVP-induced reduction in body temperature is caused partly by a reduction in the metabolic rate associated with the suppression of the lipid metabolism (243, 395). Since such changes also occurred in AH-lesion rats, it has been concluded that AVP injected peripherally does not act on the hypothalamic thermoregulatory center but on the peripheral metabolic tissues (243, 395). Similar to the in vivo findings, AVP inhibits forskolin-induced lipolysis in human adipocytes in vitro (537). These findings on AVP-induced hypothermia and the suppression of lipolysis indicate that AVP can modulate lipid metabolism in adipose tissues.

Wersinger et al. (533) reported that body temperature did not differ between V1bR-KO mice and WT mice within 30 s of the beginning of anesthesia in light conditions during the dark phase of the light/dark cycle. However, Daikoku et al. (105) reported that the body temperature measured with a biotelemetry system was lower in V1bR-KO mice than in WT mice under basal conditions. Furthermore, the body temperature decrease of V1bR-KO mice under water deprivation conditions was maintained for 48 h (stress-induced condition), and it was significantly larger for V1bR-KO mice than for WT mice. These findings suggest that the V1b receptor may be, at least in part, involved in body temperature regulation.

V. THERAPEUTIC POTENTIAL

Depending on the contributions of AVP to various pathological states, pharmacological intervention by AVP agonists or antagonists can be a valuable therapeutic strategy. Recent drug development efforts focusing on the V1a and V1b receptors are summarized in this section and **TABLE 7**.

A. AVP and Its Analogs

AVP analogs, including AVP and OT, with a variety of agonistic activities have been implicated in many disease states (292, 509). Clinical use of a V2 receptor agonist, desmopressin (1-desamino-8-D-AVP), is well established for the central DI to control polyuria. V1a receptor-mediated constriction of the vascular smooth muscles and the gastrointestinal tracts has been used in the treatment of acute esophageal variceal bleeding (34, 240). Terlipressin, an AVP analog, is preferred over AVP for esophageal bleeding, because it yields fewer adverse events and is active for a longer period (161). In fact, terlipressin is the only drug that has been shown to improve survival by significantly improving bleeding control. Serious side effects observed in AVP monotherapy, and less frequently in terlipressin monotherapy, include myocardial infarction and mesenteric ischemia (94, 309, 509). Terlipressin is also potentially beneficial for hepatorenal syndrome (439), but further trials are needed to find the patients for whom terlipressin therapy is indicated (321, 409).

Table 7. *Clinical trials of V1a and V1b vasopressin receptor antagonists*

Receptor Subtype	Antagonist (Generic Name)	Lab Where Developed	Studies	Clinical Indications	Number of Patients	References Nos.
Selective to V1a	SR-49059 (relcovaptan)	Sanofi-Synthelabo (Sanofi-Aventis)	Clinical trial (RCT)	Preterm labor	18	465
				Nonpregnant women	16	466
			Clinical trial (RCT)	Dysmenorrhea	73	71
			Placebo-controlled, double-blind, crossover trial	Healthy women	12	62
			Case study*	Diabetes insipidus	5	45
			Clinical trial (RCT)	Primary aldosteronism	8 Aldosteronism, 4 Hyperaldosteronism	402
			Clinical trial (phase I)	Healthy subjects	50	72
	SRX-251	Azevan	Clinical trial (RCT, phase I)	Healthy women	77	ClinicalTrials.gov Identifier: NCT00461370
			Clinical trial (RCT, phase I)	Healthy volunteers	50	ClinicalTrials.gov Identifier: NCT00532467
Selective to V1b	SSR-149415 (nelivaptan)	Sanofi-Synthelabo (Sanofi-Aventis)	Phase II clinical trial	Depression and anxiety		terminated

*SR49059 and YM087 restored cell surface expression of the mutant receptor. RCT, randomized clinical trial.

To maintain BP, the vasoconstrictor effects of AVP and its analogs have been the subject of intensive research. The clinical use of AVP was examined as a treatment for catecholamine-refractory septic shock (288, 289), and as an adjunct to cardiopulmonary resuscitation (93, 530). In a randomized multicenter trial (VASST, vasopressin versus norepinephrine infusion in patients with septic shock), patients with septic shock who were receiving a minimum of 5 μg/min NE were further given a low-dose of AVP (0.01–0.03 U/min) or NE (5–15 μg/min) (433). The resultant mortality rates did not differ between the two groups. Therefore, at present, absolute evidence for the usefulness of AVP in septic shock patients is not yet available. However, in the prospectively defined stratum of less severe septic shock, the mortality rate at 28 days was lower in the AVP group than in the NE group, and posthoc analyses of the VASST data indicate that AVP may reduce the risk of renal failure (182, 534). When the effectiveness of terlipressin was compared with that of AVP and NE as a first-line therapy for the treatment of septic shock in the TERLIVAP (terlipressin versus vasopressin in septic shock) study, terlipressin was associated with a reduced rate of additional NE infusion, compared with the control group. This result was, however, not found in the AVP group (295, 349). One of the pharmacological differences between AVP and terlipressin is in their pharmacokinetics (115, 534). The half-life of terlipressin is longer than that of AVP: 6 h for terlipressin versus 15–20 min for AVP (534). There is also a difference in ligand selectivity: terlipressin binds with higher affinity to the V1a receptor than to the V2 receptor, but AVP binds equally to both receptors. These pharmacological properties of terlipressin seem beneficial for the treatment of septic shock. Compared with the defined clinical applications of AVP agonists directed to V1a and V2 receptors, the clinical utility of V1b receptor agonists remains to be clarified, although synthetic ligands against V1b receptors have been developed recently and knowledge is accumulating (98, 323).

B. V1a and V1b Receptor Antagonists

While the number of synthetic AVP agonists is limited, many peptide antagonists for AVP receptors have been developed since the 1960s (323). These receptor antagonists are considered to be useful in clinical conditions associated with abnormal water retention or vasoconstriction mediated by inappropriately elevated levels of circulating AVP. Such high AVP levels are seen in patients with heart failure, SIADH, cirrhosis of the liver, polycystic kidney disease, nephrotic syndrome, surgical stress, and some forms of hypertension (18). Although peptide agonists and antagonists are considered to be difficult to formulate for oral consumption, desmopressin is now available in a tablet form for oral administration (18, 294, 323). In addition to the peptide antagonists, several nonpeptide AVP receptor antagonists have been developed. The orally and intravenously active non-

peptide AVP receptor antagonists are called "vaptans," and some of them have been applied to the treatment of various diseases or pathological conditions. Antagonists for V1a or V1b receptors tested in clinical studies are listed in **TABLE 7**.

SR49059 (relcovaptan) and YM218 are antagonists that act on the V1a receptor. Clinical studies have demonstrated that SR49059 has favorable effects in patients suffering from dysmenorrhea (71), X-linked nephrogenic DI (45), and primary aldosteronism (402) and in women receiving tocolytic treatment (113, 465). Although SR49059 was useful in proving the beneficial effects of V1a receptor antagonists and it has a good safety profile (72), the phase II study of SR49059 has been discontinued (323, 453). SRX251 is a new V1a receptor antagonist (153) and is under clinical evaluation in a recently completed phase I study (ClinicalTrials.gov; identifiers: NCT00461370 and NCT00532467).

V1a antagonists have also been examined in animal models for the treatment of other disease states such as heart failure, cerebral vasospasm, brain edema, and gastric ulcers (294, 322, 549). Furthermore, in vitro studies have suggested a potential clinical application for V1a antagonists in treating cancer or renal disease (266, 399, 479).

SSR149415 (nelivaptan) is a V1b receptor antagonist that has had beneficial effects in treating animal models of psychiatric disorders (187, 188, 451). A clinical trial of SSR149415, however, was discontinued due to its limited efficacy (271, 429). Other studies suggest potential applications of V1b antagonists for treating ACTH-secreting tumors, Cushing's syndrome, and gastrointestinal diseases (30, 109, 152, 283). ORG52186 has recently been reported to be a selective V1b receptor antagonist (103, 296), and it has been found to be effective in animal models for suppressing stress responses mediated by the pituitary V1b receptor (430, 462, 463).

Herein, we focus mainly on the effects of blocking V1a or V1b receptors in various clinical settings. The development and progress on V2 receptor antagonists can be found in other excellent reviews (113, 151, 323, 416).

C. Clinical Implications of V1a Receptor Antagonists

1. Preterm labor and dysmenorrhea

OT and AVP potently induce myometrial contractions by stimulating the OT receptors and V1a receptors in the uterus (10, 178). In spontaneous preterm labor, regular, painful, and synchronous uterine contractions occur before 37 wk of gestation (459). A desamino-OT analog, atosiban, is a competitive OT and V1a receptor antagonist used for the treatment of preterm labor (190, 317). The intravenous infusion of atosiban led to a significant decline in the frequency of uterine contractions in a randomized placebo-controlled trial (181, 516). When the effectiveness and safety of atosiban in tocolytic therapy was compared with conventional β-adrenergic receptor agonists in a double-blind, comparative-controlled study, atosiban was found to be as effective as the β-adrenergic receptor agonists and had fewer maternal side effects, especially in terms of adverse cardiovascular events (191–193, 306). A randomized controlled clinical study is needed to compare the effectiveness of atosiban versus a calcium channel blocker (438). Both atosiban and SR49059 have a high affinity for the V1a receptor (K_i = 4.7 and 7.2 nM, respectively), and a moderate affinity for the OT receptor (K_i = 397 and 340 nM, respectively) (11). Clinical studies have demonstrated that SR49059 inhibited uterine contraction not only in nonpregnant women but also in pregnant women with preterm labor (62, 465, 466). When SR49059 was administered at a single dose of 400 mg to women with preterm labor (465), the frequency of uterine contractions significantly decreased in the SR49059 group, but not in the placebo group. However, it has been reported that moderate amounts of SR49059 are transferred from the maternal to fetal circulation (285).

Primary dysmenorrhea is caused by excessive uterine muscle contractions. Thus agents that block uterine contractility such as OT/V1a receptor antagonists, nitric oxide, and calcium channel blockers may be effective in the treatment of this disorder (10, 406, 466). The plasma concentration of OT was found to be significantly higher at menstruation, and that of AVP was found to be significantly lower at ovulation in dysmenorrheic women than in healthy women (304). AVP administration was found to increase pain in women with dysmenorrhea, which was alleviated by atosiban (303). Both OT and AVP also cause potent and long-lasting vasoconstriction of the uterine arteries. The resulting ischemia may be involved in the pathogenesis of primary dysmenorrhea. The effect of AVP on uterine contractions is relatively enhanced in nonpregnant women. Correspondingly, the expression of the AVP receptor in the nonpregnant uterus is about five times higher than that of the OT receptor (12). One therapeutic effect of SR49059 can be seen in the prevention of dysmenorrhea when it is given shortly before the onset of menstruation (71).

2. Cerebral vasospasm and brain edema

AVP may play a role in the development of cerebral vasospasm and/or brain edema. In stroke patients, mean 24-h plasma AVP levels are higher than in control subjects and correlate with the severity score of the neurological deficit and the mean size of the lesion (42). In a controlled cortical impact model of brain injury, AVP synthesis was increased in activated microglia and macrophages and in the hypothalamus and cerebral cortex adjacent to the posttraumatic lesion (477).

In a rat model of subarachnoid hemorrhage (SAH), acute cerebral vasospasm was prevented by an AVP antagonist and AVP antiserum (114). SR49059 significantly reduced cerebral vasospasm after SAH induction in rats (507). Inhibition of 5-lipoxygenase attenuated the AVP-induced contraction of basilar arterial strips in both control and SAH groups. These results suggest that pathological cerebral vasospasms observed in SAH rats are due, at least in part, to the promoted 5-lipoxygenase activities stimulated by endogenous AVP. Therefore, SR49059 may represent a potential therapeutic agent in the treatment of cerebral vasospasms (373, 507). It should be noted that a part of the intracranial artery causes vasodilatation upon AVP stimulation in an endothelium-dependent manner (264, 386). This dilatation is partly blocked by the mixed V1a/OT antagonist $d(CH_2)_5[Tyr(Me)^2]AVP$ (264).

Cerebral edema is a devastating consequence of brain injury that leads to compromised cerebral blood flow and worsening parenchymal damage. Blockade of the V1a receptor by SR49059 has been shown to significantly reduce intracranial pressure or cerebral edema after cortical contusion injury, intracerebral hemorrhage injury, or cerebral artery occlusion in animal models (275, 322, 384, 457, 487). Likewise, the V1a/V2 receptor antagonist YM087 (conivaptan) significantly reduced intracranial pressure and cerebral edema after traumatic brain injury (122, 168). These findings suggest that blockade of the V1a or V1a/V2 receptor is a promising treatment strategy for treating brain edema.

3. Tumors

AVP promotes cell proliferation and/or growth by stimulating protein synthesis via the V1a receptor in several cell types including tumor cells. In vitro studies have shown that the proliferative effects of AVP on cells derived from tumors are inhibited by SR49059 (relcovaptan) (266, 399). Since the V1a receptor is widely expressed in various malignant cells, including neuroendocrine tumors (378) and small cell lung cancer (319), the AVP/V1a axis may represent a novel target for antitumor therapies.

4. Pharmacological chaperones for mutant V2 receptors

Malfunctioning mutant V2 receptors cause *X*-linked nephrogenic DI (162). The missense mutations mostly found in the *AVPR2* gene produce mutant receptors, which are misfolded, trapped in the ER, and unable to reach the basolateral cell surface where AVP binds to the receptor (350). Pharmacological compounds have been shown to rescue misfolded mutant V2 receptors in cultured cells expressing mutant V2 receptors (351). The selective nonpeptide V2 receptor antagonists SR121463A and VPA-985 (lixivaptan) increased cell surface expression and restored the signaling activity of seven naturally occurring *AVPR2* mutations (185_193del, L59P, L83Q, Y128S, S167L, A294P, and P322H). Thus these compounds work as chaperone molecules and promote the proper folding and maturation of the mutant receptors (351). In addition to these V2 receptor antagonists, the V1a receptor antagonist SR49059 (relcovaptan) and the mixed V1a/V2 antagonist YM087 (conivaptan) also restored the plasma membrane expression and signaling of a number of mutant V2 receptors. Oral administration of the V1a receptor antagonist SR49059 resulted in a decrease in urine output and an increase in urine osmolarity (45). An in vitro study also demonstrated that SR49059 works as a pharmacological chaperone ligand to rescue misfolded intracellularly localized V1a receptor mutants (206).

D. Clinical Implications of V1b Receptor Antagonists

1. Depression and anxiety

V1b receptors are implicated in affective and stress-related disorders such as depression and anxiety (451, 533). SSR149415 (nelivaptan) ameliorated the degradation of the physical state, anxiety, despair, and the loss of coping behavior produced by stress (55, 186, 223, 241, 391, 436, 450). In support of these findings, V1bR-KO mice showed attenuated stress responses (132). These findings point to a role of AVP in the modulation of emotional processes via the V1b receptor and suggested that its blockade may represent a novel possibility for the treatment of affective disorders (186, 450). However, phase II clinical trials of SSR149415 were reported to have failed (271, 429). A new V1b receptor antagonist, ABT-436, shows subnanomolar affinity for the human V1b receptor and a phase I clinical study has been completed (429).

2. Stress-induced cognitive impairment

The effects of SSR149415 (nelivaptan) on stress-induced deficits in cognitive performances were investigated in mice by a modified object recognition test. The cognitive impairment in stressed mice was prevented by the administration of SSR149415, suggesting that inhibiting V1b receptors by SSR149415 may reduce the cognitive deficits following exposure to stress-related events (514).

3. Gut inflammatory diseases

V1b receptors are localized in normal and inflamed colon tissues in humans and rats, and it has been suggested that these receptors modulate several gut functions. SSR149415 (nelivaptan) has been shown to suppress the effect of AVP on paracellular permeability and stress-induced visceral hyperalgesia, suggesting the potential application of V1b receptor antagonists in gut inflammatory diseases (152).

Knowledge of the AVP system gained by basic research is now being applied to many clinical fields that extend beyond the original antidiuretic actions on DI. Currently, peptide agonists and nonpeptide antagonists are being examined in clinical trials. To delineate the true potential of the AVP receptor system in the clinical setting, both early translational research and well-organized clinical studies are needed.

VI. CONCLUSION

The difficulty of identifying specific ligand-receptor interactions at the molecular level may become evident in research on AVP and OT, because these native agonists have various effects on the multiple subtypes of AVP and OT receptors. In a native tissue, more than one type of AVP and OT receptor might be expressed in a cell. In such cases, we now know that all combinations of the four subtypes of AVP and OT receptors can form homomeric and heteromeric receptor dimers, at least under optimum and reconstituted conditions. Although the functional importance of dimer and even oligomer receptor complexes needs to be explored in more detail, a wealth of knowledge has been accumulated since the discovery of the active posterior pituitary extract, and the progressively improving chemical tools related to AVP and OT receptors are of great help in exploring these receptor functions. In addition, genetically modified rodents can be used to show the specific consequences of the loss-of-function of single or multiple gene(s). Thus receptor knockout mice and antagonists provide complementary information on receptors. Further research with these tools should reveal the roles of V1a and V1b receptors under diverse physiological and pathophysiological conditions.

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DISCLOSURES

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