International Union of Pharmacology. XVIII.

Nomenclature of Receptors for Vasoactive Intestinal Peptide and Pituitary Adenylate Cyclase-Activating Polypeptide

ANTHONY J. HARMAR, AKIRA ARIMURA, ILLANA GOZES, LAURENT JOURNOT, MARC LABURTHE, JOSEPH R. PISEGNA, STEPHEN R. RAWLINGS, PATRICK ROBBERECHT, SAMI I. SAID, SUNIL P. SREEDHARAN, STEPHEN A. WANK, AND JAMES A. WASCHEK

MRC Brain Metabolism Unit (A.J.H) Royal Edinburgh Hospital, Edinburgh, Scotland; US-Japan Biomedical Research Laboratories (A.A.), Tulane University Medical Center, Belle Chasse, Louisiana; Department of Clinical Biochemistry (I.G.), Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel; CNRS UPR 9023 (L.J.), CCIPE, F-34094 Montpellier, France; INSERM U 410 (M.L.), Faculté de Médecine Xavier Bichat, Paris, France; CURE:VA/UCAL DDRC (J.R.P.), West Los Angeles VA Medical Center, University of California, Los Angeles, California; Life Science Resources (S.R.R.), Abberley House, Great Shelford, Cambridge, England; Laboratoire de Chimie Biologique et de la Nutrition (P.R.) Université Libre de Bruxelles, Bruxelles, Belgium; School of Medicine (S.I.S.), State University of New York at Stony Brook, Stony Brook, New York; Department of Medicine (S.P.S.), Division of Allergy and Immunology, University of California San Francisco, San Francisco, California; Digestive Diseases Branch (S.A.W.), NIDDK, National Institutes of Health, Bethesda, Maryland; Department of Psychiatry and Mental Retardation Research Center (J.A.W.), University of California Los Angeles, Los Angeles, California

I. Introduction ........................................................................... 265
II. The VPAC₁ receptor ................................................................ 266
III. The VPAC₂ receptor ............................................................... 267
IV. The PAC₁ receptor ................................................................. 267
V. Proposed nomenclature ........................................................... 267
VI. Unresolved issues and conclusions ........................................ 268
VII. Acknowledgments .................................................................. 268
VIII. References ........................................................................... 268

I. Introduction

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are members of a superfamily of structurally related peptide hormones that includes glucagon, glucagon-like peptide, secretin, and growth hormone-releasing factor (GRF). At least three receptors for PACAP exist in mammals, two of which are also high-affinity receptors for VIP. This report, prepared by the IUPHAR Subcommittee on Nomenclature for Receptors for VIP and PACAP, proposes a scheme of nomenclature for these receptors (table 1).

VIP, first isolated from porcine intestine as a 28 amino acid peptide capable of inducing vasodilation in the canine femoral artery (Said and Mutt, 1970, 1972), subsequently has been shown to have many other actions as a neuroendocrine hormone and putative neurotransmitter. The presence of VIP and specific VIP binding sites in defined pathways in the brain indicates that it may play an important role in central nervous system (CNS) function (Besson et al., 1986; Martin et al., 1987). VIP also may promote neuronal survival (Brenneman and Eiden, 1986) and regulate glycogen metabolism in the cerebral cortex (Sorg and Magistretti, 1992). VIP stimulates prolactin secretion from the pituitary (Reichlin, 1988) and catecholamine release from the adrenal medulla (Malhotra et al., 1988); in the immune system it inhibits mitogen-activated proliferation of T cells by inhibiting interleukin-2 production (Ottaway, 1987). Other actions of VIP include stimulation of electrolyte secretion, smooth muscle relaxation, and protection against oxidant injury (Gozes and Brenneman, 1989; Laburthe et al., 1993; Said, 1991, 1996). In common with the precursors of several other neuroendocrine peptides, the VIP precursor polypeptide (prepro-VIP) contains sequences encoding additional biologically active peptides, including peptide histidine isoleucine (PHI; Tatemoto and...
Mutt, 1981), peptide histidine methionine (PHM, the human equivalent of PHI; Itoh et al., 1983), and peptide histidine valine (PHV), a C-terminally extended form of PHI and PHM (Yiangou et al., 1983), and peptide histidine valine (PHV), a C-terminally extended form of PHI and PHM (Yiangou et al., 1983). PHI, PHM, and PHV probably exert their actions through the same receptors as VIP; there presently is little evidence for the existence of distinct receptors selective for these peptides.

PACAP first was identified as a 38 amino acid peptide (PACAP-38) from ovine hypothalamus that stimulated adenylyl cyclase in rat anterior pituitary cells in culture (Miyata et al., 1989). Subsequently, a C-terminally truncated, 27 amino acid form of the peptide (PACAP-27) was isolated from the same source (Miyata et al., 1990). In the CNS, PACAP, and the messenger ribonucleic acid (mRNA) encoding its precursor are most abundant in the hypothalamus, with lower levels in many other brain regions (Ghatei et al., 1993). PACAP is also present in several peripheral tissues, including the gastrointestinal tract, adrenal gland, and testis (Arimura and Shioda, 1995; Ghatei et al., 1993). Although first isolated as a hypophysiotropic hormone, the role of PACAP in the regulation of pituitary hormone secretion is still poorly understood (Rawlings and Hezareh, 1996). However, in the CNS, PACAP released from retinal afferents to the rat suprachiasmatic nucleus has been proposed to function as a daytime regulator of the biological clock (Hannibal et al., 1997), and in the periphery, PACAP is thought to function as a noncholinergic neurotransmitter stimulating catecholamine secretion from the adrenal medulla (Przywara et al., 1996) and to regulate exocrine and endocrine secretion from the pancreas (Yada et al., 1994).

Ligand binding studies (Shivers et al., 1991) suggested the existence of at least two distinct receptors for PACAP, one with much greater affinity for PACAP than for VIP (the “PACAP type I receptor”) and a second with high affinity for both PACAP and VIP (the “PACAP type II receptor”). Based on the relative potencies of natural and synthetic VIP analogues, it was later suggested that two types of high affinity VIP (PACAP type II) receptors existed in rat and human tissues. In addition to the “classical” VIP receptors from intestinal cells (Laburthe et al., 1983), a second receptor was identified in the human SUP-T1 lymphoblast cell line (Robberecht et al., 1988) and in lung cancer cell lines (Luis and Said, 1990). Subsequently, three high-affinity receptors for VIP and PACAP have been cloned.

II. The VPAC1 Receptor

The first recombinant receptor for VIP and PACAP to be identified was isolated from rat lung by Ishihara et al. (1992); the human homolog of this receptor also has been cloned and expressed in cell lines (Couvineau et al., 1994; Sreedharan et al., 1993). No splice variants of the receptor have been described to date. This receptor, originally described as the VIP receptor, subsequently was designated the VIP1 receptor (Lutz et al., 1993), the VIP/PACAP type II receptor (Ciccarelli et al., 1994), or PVR2 (Rawlings et al., 1995), and in our nomenclature is classified as the VPAC1 receptor. There are important differences between species in the pharmacology of VPAC1 receptors (Couvineau et al., 1996). When expressed in cell lines, the recombinant rat VPAC1 receptor recognized VIP (IC50, 1 nM), PHI, and PHV (IC50, 3 nM), PACAP-27 and PACAP-38 (IC50, 1 nM), and with lower affinity, GRF (IC50, 80 nM) and secretin (IC50, 300 nM). The human receptor differed from the rat receptor in its low affinity for PHI and PHV (IC50, 1000 nM and 3000 nM, respectively) and for secretin (IC50, 1500 nM). Two highly selective VPAC1 receptor agonists have been described. The VIP/GRF hybrid [Lys15, Arg16, Leu27]VIP(1–7)GRF(8–27)-NH2 (IC50, 1 nM) is a selective VPAC1 receptor agonist that does not activate GRF receptors (Gourlet et al., 1997b). [Arg16] chicken secretin (IC50, 2 nM; Gourlet et al., 1997b) is an agonist of both VPAC1 receptors and secretin receptors, but can be used as a highly selective VPAC1 receptor agonist in brain and in other tissues that do not express the secretin receptor. [Acetyl-His1, d-Phe5, Lys15, Arg16] VIP (3–7)GRF(8–27)-NH2 behaves as a selective antagonist of

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Receptor subtype</th>
<th>Gene name (HUGO)</th>
<th>Human chromosome location</th>
<th>Selective agonists</th>
<th>Selective antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC1</td>
<td>ADCYAP1R1</td>
<td>7p14</td>
<td>Maxadilan</td>
<td>PACAP(6–38)~</td>
</tr>
<tr>
<td>VPAC1</td>
<td>VIPR1</td>
<td>3p22</td>
<td>[Arg15]chicken secretin~</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VIP, VIP1</td>
<td></td>
<td>[K15R16L27]VIP(1–7)GRF(8–27)-NH2</td>
<td>VIP3–7(GRF(8–27)-NH2</td>
</tr>
<tr>
<td>VPAC2</td>
<td>VIP2, VIP3, PVR2</td>
<td>7q36.3</td>
<td>Ro 25-1553</td>
<td>—</td>
</tr>
</tbody>
</table>

~ Selective only in rodent tissues (e.g., brain) that do not express the secretin receptor.
rat and human VPAC₁ receptors (IC₅₀, 1 to 10 nM; Gourlet et al., 1997a).

Messenger RNA encoding the VPAC₁ receptor is widely distributed in the CNS, most abundantly in the cerebral cortex and hippocampus (Ishihara et al., 1992; Usdin et al., 1994), in peripheral tissues including liver, lung, and intestine (Ishihara et al., 1992; Sreedharan et al., 1995; Usdin et al., 1994) and in T lymphocytes (Delgado et al., 1996). The distribution in rat brain of binding sites for radioiodinated [Arg¹⁶]chicken secretin, a selective VPAC₁ receptor agonist, is similar to that of VPAC₁ receptor mRNA (Vertongen et al., 1997).

III. The VPAC₂ Receptor

A second receptor that responds to VIP and PACAP with comparable affinity (“PACAP type II pharmacology”) first was cloned from the rat olfactory bulb by Lutz et al. (1993) and later published independently by Usdin et al. (1994). cDNA sequences of the cognate mouse (Inagaki et al., 1994) and human (Adamou et al., 1995; Svoboda et al., 1994a; Wei and Mojsov, 1996) receptors have been published. No splice variants of the receptor have been described to date. This receptor, previously designated the VIP₂ receptor (Lutz et al., 1993), PACAPR-3 (Inagaki et al., 1994), or PVR3 (Rawlings et al., 1995), is classified in our nomenclature as the VPAC₂ receptor. When expressed in cell lines, the recombinant rat and human VPAC₂ receptors recognized VIP (IC₅₀, 3 to 4 nM), PHI, and PHV (IC₅₀, 10 to 30 nM), PACAP-27 (IC₅₀, 10 nM) and PACAP-38 (IC₅₀, 2 nM), and also recognized GRF and secretin with a very low affinity (IC₅₀, 5000 to 30,000 nM). Two cyclic peptides that have highly selective agonists of the VPAC₂ receptor have been described: Ro 25–1553 (Inagaki et al., 1994) and Ro 25–1392 (Xia et al., 1997). No selective VPAC₂ receptor antagonist has been described to date.

In the CNS, the highest concentrations of messenger RNA encoding the VPAC₂ receptor are found in the thalamus and suprachiasmatic nucleus (SCN) and lower levels in the hippocampus, brainstem, spinal cord, and dorsal root ganglia (Sheward et al., 1995; Usdin et al., 1994). The distribution in brain of binding sites for the selective VPAC₂ receptor agonist Ro 25–1553 is similar to that of VPAC₂ receptor mRNA (Vertongen et al., 1997). The receptor is also present in several peripheral tissues, including pancreas, skeletal muscle, heart, kidney, adipose tissue, testis, and stomach (Adamou et al., 1995; Krempels et al., 1995; Usdin et al., 1994; Wei and Mojsov, 1996).

IV. The PAC₁ Receptor

In 1993, Pisegna and Wank (1993) reported the cloning and expression of a PACAP-selective (type I) receptor from the rat pancreatic acinar carcinoma cell line AR4–2J. Within a few weeks, several other groups independently reported the sequence of the rat receptor (Hashimoto et al., 1993; Hosoya et al., 1993; Morrow et al., 1993; Spengler et al., 1993; Svoboda et al., 1993) and complementary deoxyribonucleic acid (cDNA) sequences of the cognate mouse (Hashimoto et al., 1996b, b) bovine (Miyamoto et al., 1994), and human (Ogi et al., 1993a) receptors have been published. This receptor (previously the PACAP type I receptor or PVR1; Rawlings et al., 1995) is classified in our nomenclature as the PAC₁ receptor. When expressed in cell lines, the recombinant rat and human PAC₁ receptors recognized PACAP-27 and PACAP-38 (IC₅₀, 1 nM) with higher potency than VIP (IC₅₀, 1000 nM) and bound PHI, PHV, secretin, and GRF with even lower affinities (Ciccarelli et al., 1995; P. Robberecht, unpublished data). Maxadilan, a 61 amino acid peptide from sand flies, with no evident sequence homology with PACAP, activates PAC₁ receptors with a high affinity (IC₅₀, 1 to 3 nM) and does not have a significant affinity for VPAC₁ or VPAC₂ receptors (Moro and Lerner, 1997). The PACAP fragment, PACAP(6–38) is a potent antagonist of PAC₁ receptors (Kᵢ, 14 nM) and does not interact with VPAC₁ receptors. However, it has a significant affinity for VPAC₂ receptors (Dickinson et al., 1997). Messenger RNA encoding the PAC₁ receptor is expressed predominantly in the CNS (most abundantly in the olfactory bulb, thalamus, hypothalamus, the dentate gyrus of the hippocampus, and granule cells of the cerebellum; Hashimoto et al., 1993, 1996a; Spengler et al., 1993) and in the adrenal medulla (Moller and Sundler, 1996).

V. Proposed Nomenclature

The nomenclature in table 1 takes account of the following considerations: (i) the PAC₁ receptor does not respond to physiological concentrations of VIP and hence the PVR nomenclature proposed by Rawlings (Rawlings et al., 1995) seems inappropriate for this receptor; (ii) the scheme permits the naming of any second PACAP specific receptor (encoded by a different gene) that may be identified as PAC₂; (iii) the scheme minimizes possible confusion with the PVR1/PVR2/PVR3 nomenclature; (iv) the scheme accords priority to VIP, consistent with the fact that, when first cloned, the PAC₁ and VPAC₂ receptors were named as receptors for VIP rather than PACAP; (v) the scheme minimizes possible
confusion with vasopressin receptors, which an alternative (VIP, V2P) scheme that we considered does not.

VI. Unresolved Issues and Conclusions

There are several unresolved issues that may change our view of the receptors in this family and may lead to future changes in nomenclature. The discovery of any new receptors for VIP and PACAP, or of any novel endogenous ligands for these receptors, would lead us to re-evaluate the scheme of nomenclature proposed here.

Gozes and colleagues have described several VIP analogues with potent activity in vitro and in vivo including (i) a hybrid peptide, combining a portion of VIP with a portion of neurotensin, that antagonized some of the behavioral actions of VIP (Gozes et al., 1989; Hill et al., 1991), inhibited the growth-promoting actions of VIP on the mouse embryo (Gressens et al., 1993, 1994) and on a variety of cell lines (Lilling et al., 1994; Moody et al., 1993; Wollman et al., 1993), and inhibited binding of VIP to some cell types but not to others (Gozes et al., 1989, 1991) and (ii) a lipophilic analogue of VIP (stearyl-Nle17-VIP; Gozes et al., 1994) which has been reported to enhance survival of neurons in culture with 100-fold greater potency than VIP (Gozes et al., 1995) and to be neuroprotective in animal models of Alzheimer's disease (Gozes et al., 1996). The nature of the receptors through which these peptides exert their actions, whether novel or existing, remains to be established.

There is apparent heterogeneity of PAC1 receptors in tissues and cell lines, where two types of "PACAP type I" pharmacology have been observed: type IA receptors, with high affinity for both PACAP-27 and PACAP-38, and type IB receptors, with high affinity for PACAP-38 but low affinity for PACAP-27 (Robberecht et al., 1991; Shivers et al., 1991). The difference between the two receptor subtypes may reflect differences in G protein coupling and second-messenger mechanisms (Van Rampilbergh et al., 1996) or result from alternative splicing of PAC1 receptor mRNA (Pantaloni et al., 1996; Spengler et al., 1993). Unlike the VPAC1 and VPAC2 receptors, the PAC1 receptor has numerous splice variants for which no systematic scheme of nomenclature has yet been devised. Splice variants either containing or lacking each of two alternative exons ("hip" and "hop") exist within the part of the PAC1 receptor cDNA encoding the third intracellular loop. The "hop" exon exists in two forms ("hop1" and "hop2") as the result of the existence of two alternative splice acceptor sites three nucleotides apart. Thus, six possible splice variants which differ in their intracellular signal transduction pathways can be generated (Journot et al., 1995; Spengler et al., 1993). Four variants of the human PAC1 receptor (null, SV-1, SV-2, and SV-3) resulting from alternative splicing of sequences equivalent to hip and hop1 also have been described (Pisegna and Wank, 1996) and shown to differ in their ability to activate phospholipase C. In addition, splice variation in the N-terminal extra-cellular domain of the mouse PAC1 receptor, leading to a 21 amino acid deletion, has been reported to influence receptor selectivity with respect to PACAP-27 and -38 binding and to change the relative potencies of the two agonists in phospholipase C stimulation (Pantaloni et al., 1996). The significance of a novel PACAP receptor variant, designated PACAPR TM4 (transmembrane domain IV), reported to differ from the previously cloned short form of the PAC1 receptor primarily by discrete sequences located in transmembrane domains II and IV (Chatterjee et al., 1996), remains to be established.

We hope that our proposals will gain acceptance and will facilitate the communication of new findings in this rapidly developing field.

Acknowledgments. We thank Drs. T.I. Bonner and S.P. Watson for liaison with the IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) and Dr. D. Girdlestone for helpful advice and assistance.

REFERENCES


